

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07F 19/00, 15/00, C07B 61/00, C08F 4/70		A1	(11) International Publication Number: WO 98/03521
			(43) International Publication Date: 29 January 1998 (29.01.98)
(21) International Application Number: PCT/US97/13312		Apartment C, 435 Encinal Avenue, Menlo Park, CA 94025 (US). BOUSSIE, Thomas [US/US]; 462 Ravenswood, Menlo Park, CA 94025 (US). TURNER, Howard [US/US]; 2948 Massih Court, Campbell, CA 95008 (US). VAN BEEK, Johannes, A., M. [NL/US]; 75 Tyrella Court, Mountain View, CA 94043 (US). MURPHY, Vince [GB/US]; 20800 Homestead Road #11F, Cupertino, CA 95014 (US). POWERS, Timothy [US/US]; 111 Adams Ranch Road, Walnut Creek, CA 94595 (US). (74) Agents: GARRETT-WACKOWSKI, Eugenia et al.; Townsend and Townsend and Crew LLP, 8th floor, Two Embarcadero Center, San Francisco, CA 94111 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM). European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(22) International Filing Date: 22 July 1997 (22.07.97)			
(30) Priority Data: 60/016,102 23 July 1996 (23.07.96) US 60/028,106 9 October 1996 (09.10.96) US 60/029,255 25 October 1996 (25.10.96) US 60/035,366 10 January 1997 (10.01.97) US Not furnished 9 June 1997 (09.06.97) US			
(60) Parent Application or Grant			
(63) Related by Continuation			
US	Not furnished (CIP)		
Filed on	Not furnished		
(71) Applicant (for all designated States except US): SYMYX TECHNOLOGIES [US/US]; 420 Oakmead Parkway, Sunnyvale, CA 94086 (US).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): WEINBERG, W., Henry [US/US]; 25 Hidden Valley Lane, Woodside, CA 94062 (US). McFARLAND, Eric [US/US]; 607 N. Third Street, San Jose, CA 95112 (US). GOLDWASSER, Isy [US/US];			
(54) Title: COMBINATORIAL SYNTHESIS AND ANALYSIS OF ORGANOMETALLIC COMPOUNDS AND CATALYSTS			
(57) Abstract			
The present invention relates, <i>inter alia</i> , to methodologies for the synthesis, screening and characterization of organometallic compounds and catalysts (e.g., homogeneous catalysts). The methods of the present invention provide for the combinatorial synthesis, screening and characterization of libraries of supported and unsupported organometallic compounds and catalysts (e.g., homogeneous catalysts). The methods of the present invention can be applied to the preparation and screening of large numbers of organometallic compounds which can be used not only as catalysts (e.g., homogeneous catalysts), but also as additives and therapeutic agents.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

**COMBINATORIAL SYNTHESIS AND ANALYSIS OF ORGANOMETALLIC
COMPOUNDS AND CATALYSTS**

This application is a continuation-in-part of Serial No. 60/_____, filed June 9, 1997 (Attorney Docket No. 016703-000340), which is a continuation-in-part of Serial No. 60/035,366, filed on January 10, 1997, which is a continuation-in-part of Serial No. 60/029,255, filed on October 25, 1996, which is a continuation-in-part of
5 Serial No. 60/028,106, filed on October 9, 1996, which is a continuation-in-part of Serial No. 60/016,102, filed on July 23, 1996, the teachings of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates, *inter alia*, to methodologies for the synthesis,
10 screening and characterization of organometallic compounds and catalysts. The methods of the present invention provide for the combinatorial synthesis, screening and characterization of libraries of supported and unsupported organometallic compounds and catalysts. The methods of the present invention can be applied to the preparation and screening of large numbers of organometallic compounds which can be used not only as
15 catalysts (*e.g.*, homogeneous catalysts), but also as additives and therapeutic agents.

BACKGROUND OF THE INVENTION

Ancillary ligand-stabilized metal complexes (*i.e.*, organometallic complexes) are useful as catalysts, additives, stoichiometric reagents, monomers, solid
state precursors, therapeutic reagents and drugs. The ancillary ligand system comprises
20 organic substituents, bind to the metal center(s), remain associated with the metal center(s), and therefore provide an opportunity to modify the shape, electronic and chemical properties of the active metal center(s) of the organometallic complex.

Certain organometallic complexes are catalysts for reactions such as oxidation, reduction, hydrogenation, hydrosilylation, hydrocyanation, hydroformylation,

polymerization, carbonylation, isomerization, metathesis, carbon-hydrogen activation, cross coupling, Friedel-Crafts acylation and alkylation, hydration, dimerization, trimerization and Diels-Alder reactions. Organometallic complexes can be prepared by combining an ancillary ligand precursor with a suitable metal precursor in a suitable solvent at a suitable temperature. The yield ACTIVITY AND SELECTIVITY of the targeted organometallic complex is dependent on a variety of factors including the form of the ancillary ligand precursor, the choice of the metal precursor, the reaction conditions (*e.g.*, solvent, temperature, time, *etc.*) and the stability of the desired product. In some cases, the resulting organometallic complex is inactive as a catalyst until it is "activated" by a third component or cocatalyst. In many cases, third component "modifiers" are added to active catalysts to improve performance. The effectiveness of the cocatalyst, the type and amount of modifier, and the suitability of the ancillary ligand precursor, metal precursor and reaction conditions to form an effective catalyst species in high yield are unpredictable from first principles. Given the number of variables involved and the lack of theoretical capability, it is not surprising that the discovery and optimization of catalysts is laborious and inefficient.

One important example of this is the field of single-sited olefin polymerization catalysis. The active site typically comprises an ancillary ligand-stabilized coordinatively unsaturated transition metal alkyl complex. Such catalysts are often prepared by the reaction of two components. The first component is an ancillary ligand-stabilized transition metal complex having a relatively low coordination number (typically between three and four). The second component, known as the activator or cocatalyst, is either an alkylating agent, a Lewis acid capable of abstracting a negatively charged leaving group ligand from the first component, an ion-exchange reagent comprising a compatible non-coordinating anion or a combination thereof. Although a variety of organometallic catalysts have been discovered over the past 15 years, this discovery is a laborious process which consists of synthesizing individual potentially catalytic materials and subsequently screening them for catalytic activity. The development of a more efficient, economical and systematic approach for the synthesis of novel organometallic catalysts and for the screening of such catalysts for useful properties would represent a significant advance over the current state of the art. A particularly promising method for

simplifying the discovery process would rely on methods of producing combinatorial libraries of ligands and catalysts and screening the compounds within those libraries for catalytic activity using an efficient parallel or rapid serial detection method.

The techniques of combinatorial synthesis of libraries of organic compounds are well known. For example, Pirrung, *et al.* developed a technique for generating arrays of peptides and other molecules using, for example, light-directed, spatially-addressable synthesis techniques (U.S. Patent No. 5,143,854 and PCT Publication No. WO 90/15070). In addition, Fodor, *et al.* have developed automated techniques for performing light-directed, spatially-addressable synthesis techniques, photosensitive protecting groups, masking techniques and methods for gathering fluorescence intensity data (Fodor, *et al.*, PCT Publication No. WO 92/10092). In addition, Ellman, *et al.* recently developed a methodology for the combinatorial synthesis and screening of libraries of derivatives of three therapeutically important classes of organic compounds, benzodiazepines, prostaglandins and β -turn mimetics (*see*, U.S. Patent No. 5,288,514).

Using these various methods of combinatorial synthesis, arrays containing thousands or millions of different organic elements can be formed (U.S. Patent Application No. 805,727, filed December 6, 1991). The solid phase synthesis techniques currently being used to prepare such libraries involve a stepwise process (*i.e.*, sequential, coupling of building blocks to form the compounds of interest). In the Pirrung, *et al.* method, for example, polypeptide arrays are synthesized on a substrate by attaching photoremovable groups to the surface of the substrate, exposing selected regions of the substrate to light to activate those regions, attaching an amino acid monomer with a photoremovable group to the activated region, and repeating the steps of activation and attachment until polypeptides of the desired length and sequences are synthesized. The Pirrung, *et al.* method is a sequential, step-wise process utilizing attachment, masking, deprotecting, attachment, *etc.* Such techniques have been used to generate libraries of biological polymers and small organic molecules to screen for their ability to specifically bind and block biological receptors (*i.e.*, protein, DNA, *etc.*). These solid phase synthesis techniques, which involve the sequential addition of building blocks (*i.e.*, monomers, amino acids) to form the compounds of interest, cannot readily be used to

prepare many inorganic and organic compounds. As a result of their relationship to semiconductor fabrication techniques, these methods have come to be referred to as "Very Large Scale Immobilized Polymer Synthesis," or "VLSIPS" technology.

5 Schultz, *et al.* was the first to apply combinatorial chemistry techniques to the field of material science (PCT WO/9611878, the teachings of which are incorporated herein by reference). More particularly, Schultz, *et al.* discloses methods and apparatus for the preparation and use of a substrate having thereon an array of diverse materials in predefined regions. An appropriate array of materials is generally prepared by delivering components of materials to predefined regions on the substrate and simultaneously
10 reacting the reactants to form different materials. Using the methodology of Schultz, *et al.*, many classes of materials can be generated combinatorially including, for example, inorganic materials, intermetallic materials, metal alloys, ceramic materials, *etc.* Once prepared, such materials can be screened for useful properties. Liu and Ellman, *J. Org. Chem.* 1995, 60:7, working in the area of asymmetric catalysis, have developed a solid-phase synthesis strategy for the 2-pyrrolidinemethanol ligand class, and have demonstrated
15 that the ligands can be directly evaluated for enantioselective additions of diethyl zinc reagent to aldehyde substrates using conventional analytical methods and not rapid parallel or serial screening methods.

From the above, it is apparent that there is a need for the development of
20 methods for synthesizing and screening libraries of organometallic materials for catalytic properties. These methods would greatly accelerate the rate discovering and optimizing catalytic process. Quite surprisingly, the instant invention provides such methods.

SUMMARY OF THE INVENTION

The present invention relates to methods for the synthesis and
25 characterization of arrays, *i.e.*, libraries of catalysts and organometallic compounds. More particularly, the methods of the present invention provide for the combinatorial synthesis, screening and characterization of large arrays or libraries of diverse supported and unsupported ligands, catalysts and organometallic compounds.

Thus, in one aspect, the present invention provides a method of making and
30 screening an array of metal-ligand compounds, the method comprising:

- (a) synthesizing a spatially segregated array of ligands;
- (b) delivering a suitable metal precursor to each element of the array of ligands to create an array of metal-ligand compounds;
- (c) optionally activating the array of metal-ligand compounds with a suitable cocatalyst;
- (d) optionally modifying the array of metal-ligand compounds with a third component; and
- (e) screening the array of metal-ligand compounds for a useful property using a parallel or rapid serial screening technique selected from the group consisting of optical imaging, optical spectroscopy, mass spectrometry, chromatography, acoustic imaging, acoustic spectroscopy, infrared imaging and infrared spectroscopy.

In yet another aspect, the invention comprises an array of between 10 and 10^6 different metal-ligand compounds at known locations on the substrate. In certain embodiments, the array will comprise more than 50 different metal-ligand compounds at known locations on the substrate. In other embodiments, the array will comprise more than 100 or more than 500 different metal-ligand compounds. In still further embodiments, the array will comprise more than 1,000, more than 10,000 or more than 10^6 different metal-ligand compounds at known locations on the substrate.

Other features, objects and advantages of the invention and its preferred embodiments will become apparent from the detailed description which follows.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1A and 1B illustrate examples of transition-metal based metallocene catalysts and catalysts based on the late transition metals, *e.g.*, zirconium and nickel, respectively.

FIGS. 2A and 2B illustrate sequences of solid-phase reactions which can be used to achieve combinatorial variations of diimine and/or diamine ligands.

FIGS. 3A and 3B illustrate various combinatorial routes for the synthesis of various ligand types.

FIGS. 4A-4G illustrate examples of ligand cores which can be made using combinatorial chemistry formats.

FIG. 5 illustrates a synthesis of an exemplary ancillary ligand on a support, wherein CN = 1 or 2, charge = 0 or -1.

FIG. 6 illustrates a synthesis of an exemplary ancillary ligand on a support, wherein CN = 1, 2 or 3, charge = 0, -1 or -2.

5 FIG. 7 illustrates a synthesis of an exemplary ancillary ligand with metal complex on a support, wherein CN = 2, charge = -2, denoted [2,2].

FIG. 8 illustrates the synthesis of two exemplary ancillary ligands off support, wherein CN = 2, charge = 0, -1 or -2.

10 FIG. 9 illustrates a synthesis of an exemplary ancillary ligand off support, wherein CN = 2, charge = -1, denoted [2,1].

FIG. 10 illustrates a synthesis of an exemplary ancillary ligand off support with a functional linker, wherein CN = 2, charge = 0, -1, -2 or -3.

FIG. 11 illustrates a synthesis of an exemplary ancillary ligand off support with a "functionless" linker, wherein CN = 2, charge = 0, -1 or -2.

15 FIG. 12 illustrates a synthesis of an exemplary ancillary ligand off support wherein CN = 2 or 3, charge = 0, -1, -2, -3 or -4.

FIGS. 13A and 13B illustrate exemplary synthetic schemes useful in the placement of acidic functionality on the R-group substituents within the array or library.

20 FIG. 14 illustrates the synthesis of a library of 48 diimine ligands which is subsequently converted to a library of 96 diimine-metal compounds.

FIG. 15 illustrates a generalized solution-phase synthesis of diimines utilizing immobilized catalysts, proton sponges and reactant adsorbing reagents.

FIG. 16 illustrates an array of commercially-available diketones of use in practicing the present invention.

25 FIG. 17 illustrates examples of immobilized Lewis acid catalysts and dehydrating reagents.

**DETAILED DESCRIPTION OF THE INVENTION
AND PREFERRED EMBODIMENTS**

TABLE OF CONTENTS

	I.	Glossary: Abbreviations and Definitions
5	II.	Assembly of Combinatorial Libraries
	A.	General Overview
	B.	Synthesis Supports and Substrates
	C.	Ligands
	D.	Linkers
10	E.	Metals
	F.	Immobilized Reagents
	G.	Non-coordinating Anions (NCA)
	H.	Diimine Catalyst Library Design and Synthesis
	III.	Screening of Combinatorial Libraries
15	IV.	EXAMPLES

I. GLOSSARY: ABBREVIATIONS AND DEFINITIONS

Abbreviations and generalized chemical formulae used herein have the following meanings: Cp, η^5 -cyclopentadienyl; Cp*, η^5 -pentamethylcyclopentadienyl; MAO, methylaluminoxane; [Q]⁺[NCA]⁻, reactive cation/non-coordinating anion compound; EDG, electron-donating group; EWG, electron-withdrawing group; DME, dimethoxyethane; PEG, poly(ethyleneglycol); DEAD, diethylazodicarboxylate; COD, cyclooctadiene; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; Fmoc, 9-fluorenylmethoxycarbonyl; HOBT, 1-hydroxybenzotriazole; BTU, O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluorophosphate; DIAD, diisopropylazodicarboxylate. Other abbreviations and chemical formulae used herein have the meaning normally assigned to them by those of skill in the art.

Catalyst: As used herein, the term "catalyst" refers to a compound which speeds a chemical reaction or causes it to occur. The catalysts of the present invention are formally organometallic compounds. Certain of the organometallic compounds of the invention will require "activation" prior to being catalytically active. Other

organometallic compounds of the invention will be "activator-free catalysts" and will not require activation prior to being catalytically active.

Ligand: Organometallic compounds are conventionally formulated as comprising a central metal atom or ion surrounded by and bonded to other atoms, ions, or small molecules known as "ligands". Ligands are either organic (*e.g.*, η^1 -aryl, alkenyl, alkynyl, cyclopentadienyl, CO, alkylidene, carbene) or inorganic (*e.g.*, Br⁻, Cl⁻, OH⁻, NO²⁻, *etc.*), and can be charged or neutral. The number of times an inorganic or organic moiety occurs as a ligand in a metallic complex is generally indicated by the prefixes di, tri, tetra, *etc.* Multiple occurrences of complex organic ligands are indicated by the prefixes bis, tris, tetrakis, *etc.*

As used herein, the term "ancillary ligand" is distinguished from a "leaving group ligand." An ancillary ligand will remain associated with the metal center(s) as an integral constituent of the catalyst or organometallic compound. Ancillary ligands are defined according to the number of coordination sites they occupy and their formal charge. A leaving group ligand is a ligand which is replaced in a ligand substitution reaction. A leaving group ligand can be replaced with an ancillary ligand or an activator component.

In most cases, the formalisms for assigning the charge on the ligand and the number of coordination sites it occupies are easily established and unambiguous. As with most chemical formalisms, there are examples where these assignments are subject to interpretation and debate. Such is the case with the η^5 cyclopentadienyl (Cp) ligand which is considered to occupy 3 or 1 coordination site(s) on the metal, depending on the overall symmetry about the metal center. When the symmetry of the metal complex is best described as octahedral, the Cp-ligand will be assigned to occupy 3-coordination sites (on face of the octahedron). If, however, the metal complex symmetry is best described as tetrahedral, square planar or trigonal, the Cp-ligand is considered to occupy 1-coordination site. For the purposes of this invention, the Cp-ligand will formally be considered to occupy 1-coordination site on the metal complex.

Activator: In general, activators are used in the synthesis of various catalysts. Activators render a metallic center active as a catalyst and can be, for example, a chemical or an energy source which renders a metal center active and which, in certain

embodiments, is directed from a source to a catalyst precursor which is located at a defined region on a substrate.

In certain embodiments wherein an activator is a chemical reagent which converts a metal complex into an olefin polymerization catalyst, the activator will generally fall into one of two broad classes of agents: (1) alkylating agents; and (2) ionizing agents.

"Alkylating agents," as used herein, define agents which function by exchanging unreactive ligands, such as, for example, halide or alkoxide, for reactive σ -bonded alkyl groups, such as, for example, methyl or ethyl groups. An example of this type of activation is illustrated by the conversion of Cp_2^*ScCl into Cp_2^*ScMe (where $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) using methyllithium. In general, activation by alkylation works in systems where the metal center of the catalyst precursor is highly coordinatively unsaturated and does not require further reduction of coordination number to function as a catalyst; however, this mode of activation is not limited to such metal centers.

"Ionizing agents" function as activators by reducing the coordination number of the transition metal precursor by at least one coordination site to form ionic products. There are two types of ionizing agents: (1) Lewis acids; and (2) ion-exchange activators.

"Lewis acids" function by abstracting a leaving group ligand from the metal center to form a compatible non-coordinating anion ("NCA" which is comprised of the leaving group ligand and the Lewis acid) and a coordinatively unsaturated active transition metal cation. "Ion-exchange activators" deliver to the catalyst precursor a preformed compatible non-coordinating anion and accept from the catalyst precursor a coordinating anion (such as a methyl or halide group). Ion-exchange activators have the general formula Q^+NCA^- , wherein Q^+ is a reactive cation and NCA^- is a compatible non-coordinating anion. The Lewis acids and ion exchange activators of use with the present invention include both soluble and supported (*e.g.*, silica resin bound) Lewis acids and ion exchangers.

In some cases, activation can also be accomplished by Lewis acid or ion-exchange agents. For example, consider two possible chemical pathways leading to the synthesis of the catalyst, $[\text{Cp}_2\text{ZrCH}_3]^+[\text{B}(\text{C}_6\text{F}_5)_3\text{CH}_3]^-$, where $[\text{B}(\text{C}_6\text{F}_5)_3\text{CH}_3]$ is the

"compatible non-coordinating anion" or "counter-ion". Using the Lewis acid pathway, the catalyst precursor is $[\text{Cp}_2\text{Zr}(\text{CH}_3)_2]$ and the activator is $[\text{B}(\text{C}_6\text{F}_5)_3]$. Using the "ion-exchange" pathway, the catalyst precursor is $[\text{Cp}_2\text{Zr}(\text{CH}_3)_2]$ and the activator is $[\text{Ph}_3\text{C}]^+[\text{B}(\text{C}_6\text{F}_5)_3\text{CH}_3]^-$. These examples demonstrate that all or part of the activator can become the "non-coordinating anion" or "counterion."

Compatible non-coordinating anion: A compatible non-coordinating anion is an anion that either does not coordinate to the metal cation, or is only weakly coordinated to the metal cation such that it remains sufficiently labile to be displaced by a neutral Lewis base or the molecule being transformed in the catalytic cycle. The term "compatible non-coordinating anion" specifically refers to an anion which when functioning as a stabilizing anion in the catalyst system of this invention does not transfer an anionic fragment to the metal cation to form inactive neutral products.

Organometallic compounds: Classically, compounds having bonds between one or more metal atoms and one or more carbon atoms of an organic group are defined as "organometallic compounds". For the purposes of this application, "organometallic" is defined to include all ancillary ligand stabilized metallic complexes regardless of presence or absence of a metal-carbon bond. As used herein, "organometallic compounds" are distinguished from catalysts by their lack of useful levels of catalytic activity in an initial screening. This definition does not, however, preclude a compound which was initially identified as an organometallic compound without catalytic activity in reference to a certain class of reactions (*e.g.*, alkene polymerization) but which is later identified as having catalytic activity with a different class of reactions (*e.g.*, alkyne polymerization).

Metallocenes: Organometallic compounds in which a transition metal, such as, for example, zirconium, cobalt or nickel, is bonded to at least one substituted or unsubstituted η^5 -cyclopentadienyl group.

Substrate: A material having a rigid or semi-rigid surface. In some embodiments, at least one surface of the substrate will be substantially flat. In other embodiments, the substrate will be divided into physically separate synthesis regions. Division of the substrate into physically separate synthesis regions can be achieved with, for example, dimples, wells, raised regions, etched trenches, or the like. In still other

embodiments, small beads or pellets may be provided on the surface by, for example, placing the beads within dimples, wells or within or upon other regions of the substrate's surface. Alternatively, the small beads or pellets may themselves be the substrate. An appropriate substrate can be made out of any material which is compatible with the processes intended to occur thereon. Such materials include, but are not limited to, organic and inorganic polymers, quartz, glass, silica, *etc.* The choice of an appropriate substrate for certain given conditions will be apparent to those of skill in the art.

Synthesis support: A material such as, for example, silica, alumina, a resin or controlled pore glass (CPG) which is functionalized to allow a ligand or a ligand component to be attached either reversibly or irreversibly thereto. Specific examples of synthesis supports include Merrifield resin and functionalized silica gel. A synthesis support can be held within or upon a "substrate." "Synthesis support," "support," "bead" and "resin" are used interchangeably herein.

Predefined region: A predefined region is a localized, addressable area on a substrate which can be used for formation of a selected material and is otherwise referred to herein in the alternative as "known" region, "reaction" region, a "selected" region, or simply a "region." The predefined region may have any convenient shape, *e.g.*, circular, rectangular, elliptical, wedge-shaped, *etc.* Additionally, the predefined region can be a bead or pellet which is coated with a reactant component(s) of interest. In this embodiment, the bead or pellet can be identified with a tag, such as, for example, an etched binary bar code that can be used to indicate the history of the bead or pellet (*i.e.*, to identify which components were deposited thereon). In general, a predefined region is from about 25 cm² to about 10 μm². In a preferred embodiment, a predefined region and, therefore, the area upon which each distinct material is synthesized is smaller than about 10 cm². In another preferred embodiment, a predefined region is less than 5 cm². In a further preferred embodiment, a predefined region is less than 1 cm². In yet a further preferred embodiment, a predefined region is less than 1 mm². In still other preferred embodiments, the regions have an area less than about 10,000 μm². In an additional preferred embodiment, the regions are of a size less than 10 μm².

Linker: As used herein, the term "linker" or "linker arm" refers to a moiety interposed between the substrate and the ligand, catalyst or the organometallic compound. Linkers are either cleavable or noncleavable.

Metal ion: As used herein, the term "metal ion" refers to ions which are
5 derived from, for example, simple salts (*e.g.*, AlCl_3 , NiCl_2 , *etc.*), complex or mixed salts comprising both organic and inorganic ligands (*e.g.*, $[(\eta^5\text{-C}_5\text{Me}_5)\text{IrCl}_2]_2$, *etc.*) and metal complexes (*e.g.*, Gd(NTA)_2 , CuEDTA , *etc.*). Metal ions of use in practicing the present invention include, for example, main group metal ions, transition metal ions, lanthanide ions, *etc.* Zero valent metal precursors, such as Ni(COD)_2 , are included in this
10 definition.

II. ASSEMBLY OF COMBINATORIAL LIBRARIES

A. General Overview

The present invention provides methods, compositions and devices used for the combinatorial synthesis, screening and characterization of supported and unsupported
15 organometallic compounds and ancillary ligand-stabilized catalysts (*e.g.*, homogeneous and heterogenous catalysts) and libraries thereof. Preferably, the synthesis and screening of such libraries is carried out in a spatially selective, simultaneous, parallel or rapid serial fashion. In the embodiment wherein the library synthesis is carried out in parallel, a parallel reactor is preferably employed. The illustrations herein provide the first
20 methods for generating and screening combinatorial libraries of organometallic compounds and catalysts.

The methods of the present invention provide for the assembly of libraries of organometallic compounds and catalysts. The catalysts of the present invention are either of a type which requires activation by an activating agent or, alternatively, they are
25 activator-free catalysts. The invention also provides methods for the synthesis of both supported and unsupported organometallic compounds and catalysts. When the library compounds are supported, they are either attached to a substrate or, alternatively, to an intermediate synthesis support which is itself optionally on or within a substrate. Supported library compounds are bound to the substrate or synthesis support either
30 directly through a functional group attached to a ligand core or, alternatively, through a

linker arm which is itself a ligand core or pendent from a ligand core. When the library comprises catalysts, the library can be assembled such that the catalysts are homogeneous, heterogenous or a mixture thereof.

Thus, in one aspect the present invention provides a method of making an array of metal-ligand compounds, the method comprising:

(a) synthesizing a first metal-binding ligand and a second metal-binding ligand on first and second regions of a substrate;

(b) delivering a first metal ion to the first metal-binding ligand and a second metal ion to the second metal-binding ligand to form first and second metal-ligand compounds.

In this embodiment, ligands are assembled on the substrate by the step-wise delivery of ligand fragments and the reagents necessary to couple those fragments. Once the ligands are synthesized, they are reacted with metal ions to form metal-ligand compounds.

In another aspect, the invention provides a method for immobilizing intact ligands on a substrate by binding the ligands to reactive groups on the surface of the substrate. Thus, in this aspect, the invention is a method for making an array of metal-ligand compounds, the method comprising:

(a) delivering a first metal-binding ligand and a second metal-binding ligand on first and second regions of a substrate;

(b) delivering a first metal ion to the first metal-binding ligand and a second metal ion to the second metal-binding ligand to form a first metal-ligand compound and a second metal ligand compound.

In another embodiment, the metal-ligand compounds thus synthesized are reacted with an activating agent. Preferred activators include, but are not limited to, Lewis acids, such as $B(C_6F_5)_3$ and MAO, and ion-exchange reagents of the form $[Q]^+[NCA]^-$, such as $[H(OEt)_2]^+[BAR_4]^-$ and $[H(OEt)_2]^+[B(C_6F_5)_4]^-$. In a still further preferred embodiment, the activators are independently selected for each member of the library. In another preferred embodiment, the activated metal-ligand compounds comprise olefin polymerization catalysts. In a further preferred embodiment, the catalysts are activator-free catalysts.

In another aspect, the invention provides a method of making and screening an array of metal-ligand compounds, the method comprising:

- (a) synthesizing a spatially segregated array of ligands;
- (b) delivering a suitable metal precursor to each element of said array of
5 ligands to create an array of metal-ligand compounds;
- (c) optionally activating said array of organometallic complexes with an activator (*e.g.*, a suitable cocatalyst);
- (d) optionally modifying said array of metal-ligand compounds with a third component; and
- 10 (e) screening said array of metal-ligand compounds for a useful property using parallel or rapid serial optical imaging and/or spectroscopy, mass spectrometry, chromatography, acoustic imaging/spectroscopy, infrared imaging/spectroscopy.

Numerous types of ligands are of use in practicing the present invention (*see*, Figs. 1-13). In a preferred embodiment, the ligands are neutral bidentate ligands.
15 In another preferred embodiment, the ligands are monoanionic bidentate ligands. In yet another preferred embodiment, the ligands are chelating diimine ligands. In still another preferred embodiment, the ligands are salen ligands. Preferred ligands have a coordination number which is independently selected from the group consisting of 1, 2, 3 and 4. These preferred ligands have a charge which is independently selected from the
20 group consisting of 0, -1, -2, -3 and -4. Certain preferred ligands have a charge which is greater than their coordination number.

The ligands are either attached directly or through a linker group to a substrate or a synthesis support or, alternatively, they are in solution. In a preferred embodiment, the ligands are attached directly to a synthesis support. In another preferred
25 embodiment, the ligands are attached to a synthesis support through a linker group. In a further preferred embodiment, the ligands are attached to a substrate either directly or through a linker.

Any of the functional groups on the ligands or the linkers, or components of the ligands or the linkers, can be protected to avoid interference with the coupling
30 reactions. The protection can be achieved by standard methods or variations thereof. A plethora of protection schemes for most known functional groups are known to and used

by those of skill in the art. See, for example, Greene, T., *et al.*, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, Second Ed., John Wiley and Sons, New York, 1991, the teachings of which are herein incorporated by reference.

The chemical synthesis steps can be conducted using solid-phase,
5 solution-phase or a combination of solid-phase and solution-phase synthetic techniques. The ligand, metal, activator, counterion, substrate, synthesis support, linker to the substrate or synthesis support and additives can be varied as part of the library. The various elements of the library are typically varied by, for example, the parallel dispensing of reagents to spatially addressable sites or by known "split-and-pool"
10 combinatorial methodology. Other techniques for assembling combinatorial libraries will be apparent to those of skill in the art. See, for example, Thompson, L.A., *et al.*, "Synthesis and Applications of Small Molecule Libraries," *Chem. Rev.* 1996, 96:555-600, and references therein which are herein incorporated by reference.

Any number of a wide range of metal ions are appropriate for use in the
15 present invention. In a preferred embodiment, the metal ions are transition metal ions. In another preferred embodiment, the metal ions are ions of Pd, Ni, Pt, Ir, Rh, Co, Cr, Mo and W. When the metal ion is a transition metal ion, in one preferred embodiment, the metal-binding ligands are neutral bidentate ligands and the transition metal ion is stabilized by a labile Lewis base in the metal precursor. In another preferred
20 embodiment, the ligands are monoanionic bidentate ligands and the transition metal center is stabilized by a labile anionic leaving group ligand in the metal precursor. In a still further preferred embodiment, the ligands are [2,2] or [2,1] ligands and each of the ligands is contacted with a main group metal alkyl complex such that the ligands are in the mono- or di-protic form. A particularly preferred metal alkyl complex is a
25 trialkylaluminum complex. In a particularly preferred embodiment, the resulting metal-ligand compounds are useful for an organic transformation requiring a Lewis acid site such as, for example, stereoselective coupling reactions, olefin oligomerization reactions and olefin polymerization reactions. In yet another preferred embodiment, the aluminum-ligand compounds are further modified with an ion-exchange activator to produce an array
30 of ligand-stabilized cationic aluminum compounds. A preferred ion-exchange activator is $[\text{PhNMe}_2\text{H}][\text{B}(\text{C}_6\text{F}_5)_4]$.

The catalysts prepared using the methods of the invention can be useful for catalyzing a wide variety of reactions including, but not limited to, oxidation, reduction, hydrogenation, hydrosilation, hydrocyanation, polymerizations (*e.g.*, olefins and acetylenes), water gas shift, oxo reaction, carboalkoxylation of olefins, carbonylation reactions (*e.g.*, of acetylenes and alcohols, *etc.*), decarbonylation, *etc.*

As explained in greater detail hereinbelow, following the synthesis of the library, the library compounds are screened for a useful property. In a preferred embodiment, the useful property is a property relating to a polymerization reaction. In another preferred embodiment, the useful property is a mechanical property, an optical property, a physical property or a morphological property. In certain preferred embodiments, the useful property is a chemical property such as, for example, the lifetime of the metal-ligand compounds, the stability of these compounds under specific reaction conditions, the selectivity of the library compounds for a particular reaction, the conversion efficiency of the library compounds in a particular reaction or the activity of the library compounds in a particular reaction. The library can be screened for compounds with useful properties using a wide range of techniques. Thus, in one preferred embodiment, the screening is performed by a method chosen from the group consisting of scanned mass spectrometry, chromatography, ultraviolet imaging, visible imaging, infrared imaging, electromagnetic imaging, ultraviolet spectroscopy, visible spectroscopy, infrared spectroscopy, electromagnetic spectroscopy and acoustic methods.

In general, the analysis of catalysts and organometallic compounds requires the ability to rapidly characterize each member to identify compounds with specific, desired properties. An exemplary use of the present invention is in the discovery and optimization of new catalysts. In a preferred embodiment wherein catalysts are synthesized, the constituents of the combinatorial library will be analyzed using high throughput methods for measuring such properties as activity (*i.e.*, turnover), selectivity in converting reactants into desired products, and stability during operation under a wide variety of substrate concentrations and reaction conditions. Spatially selective characterization methods include, for example, those capable of: (i) identification and characterization of gas phase products and volatile components of the condensed phase products; (ii) identification and characterization of condensed phase products; and (iii)

measurement of physical properties of the catalyst elements on the library. Similar high throughput methodologies can be used for measuring properties other than catalysis (*e.g.*, target binding, solubility, hydrophilicity, *etc.*) of libraries of both organometallic compounds and catalysts.

5 In yet another aspect, the invention comprises an array of between 10 and 10^6 different metal-ligand compounds at known locations on the substrate. In certain embodiments, the array will comprise more than 50 different metal-ligand compounds at known locations on the substrate. In other embodiments, the array will comprise more than 100 or more than 500 different metal-ligand compounds. In still further
10 embodiments, the array will comprise more than 1,000, more than 10,000 or more than 10^6 different metal-ligand compounds at known locations on the substrate.

 The assembly of combinatorial libraries of organometallic compounds and catalysts allows the rapid assessment of the effects of changes in numerous characteristics of the compounds themselves, the reactions used to prepare the compounds and the
15 reactions in which the compounds take part. Examples of characteristics and properties (together referred to herein as "parameters") which can be modified include, but are not limited to, the identity of the ligand core itself, substituents on the ligand core, identity and/or charge of the metal ion, counterion, activator, reaction conditions, solvents, additives, supports, substrates and linkers. Other parameters of interest whose effects can
20 be investigated by the use of the methods of the present invention will be apparent to those of skill in the art.

 In a preferred embodiment of the present invention, only one parameter is varied per addressable location. In another preferred embodiment, the compounds synthesized are catalysts and variations in the various parameters are used to identify
25 optimal species and conditions for catalyzing, or otherwise carrying out, a desired reaction or class of reactions.

 Combinatorial libraries can be used in the synthesis of both organometallic compounds and catalysts to identify the optimal metal ion, metal ion charge, geometry and/or coordination number for achieving a property of interest. Similarly, the library
30 can be used to measure the effects of changes in counterions, activators, reaction conditions, solvents and additives. Properties of the library constituents which are of

interest include, for example, catalytic parameters, solubility, conductivity, hydrophilicity, mechanical properties and general pharmacological parameters (*e.g.*, target binding, pharmacokinetics, distribution volume, clearance, *etc.*).

5 A specific example of a type of compound which can be synthesized and analyzed in a combinatorial format are the diimine Ni and Pd complexes discovered by Brookhart. This family of catalysts comprises 1,2 diimine ligand moieties bound to either 4-coordinate Ni^{2+} or Pd^{2+} centers. These precursors are then activated with a Lewis acid, such as MAO, and ion-exchange reagents of the form $[\text{Q}]^+[\text{NCA}]^-$, such as $[\text{H}(\text{OEt})_2]^+[\text{BAR}_4]^-$ and $[\text{H}(\text{OEt})_2]^+[\text{B}(\text{C}_6\text{F}_5)_4]^-$, *etc.*, to form polymerization catalysts. The
10 properties of the catalyst (*e.g.*, polymer molecular weight capability, polymer branching statistics, *etc.*) are dependent upon the choice of the constituents of the catalyst. The use of combinatorial libraries allows for the optimization of the nature of these constituents.

Combinatorial libraries can also be used to identify the optimal means of attaching an organometallic compound or a catalyst to a substrate or support (silicate, aluminate, polystyrene, *etc.*). The catalysts or organometallic compounds are attached to
15 the substrate or synthesis support directly through a functional group on a ligand or, alternatively, through a linker arm. Linker arm parameters which can be varied over a library include, for example, length, charge, solubility, conformational lability and chemical composition. Substituents of these linkers can be varied and particular combinations of catalysts, linkers, synthesis supports, metals, polymerization conditions,
20 *etc.* can then be assayed directly for optimal catalytic activity and process operability using a two-dimensional or three-dimensional array format or with bead supports.

Optimization of compound constituents such as the metal ion, counterion, activator identity and concentration, *etc.* is accomplished by varying the identity or
25 concentration of the constituent whose effect on the compound produced is being examined. Typically, the parameter will be varied over the array of addressable locations comprising the library. In addition to the above-described constituents, the nature of the substrate can also be varied using a combinatorial strategy.

The effect(s) of altering the characteristics of the constituents of a
30 combinatorial library can be analyzed either directly or indirectly. Thus, in one embodiment, the structure or properties of the library compounds themselves are studied.

In another embodiment, the effect of the library compounds on another molecule or system is studied. For example, when a library of polymerization catalysts is synthesized, the effect of variations in constituents over the library can be assessed by analyzing the polymer products produced using the constituents of the catalyst library.

5 Such analysis can examine catalyst characteristics including, for example, molecular weight capability, copolymerization capability, lifetime, comonomer compatibility, chemical stability, and ability to form polymers of differing topology, molecular weight distribution and/or microstructure. Other means of analyzing combinatorial libraries will be apparent to those of skill in the art.

10 Libraries can be synthesized on diverse substrates made of different materials or having different topological characteristics and the effect of the nature of the support on the compounds synthesized can be examined as described above. In certain embodiments, the substrate can also comprise a synthesis support.

B. Synthesis Supports and Substrates

15 In a preferred embodiment, the library comprises an array of supported metal-ligand compounds. In general, if supported organometallic compounds or catalysts are synthesized, the metal-ligand compounds are attached directly to either a substrate or a synthesis support for the library of organometallic compounds or catalysts. In other embodiments, the metal-ligand compounds are attached to the substrate or synthesis support via a linker-arm.

20 The structure, shape and functional characteristics of the substrate are limited only by the nature and scale of the reactions performed using the substrate. In certain embodiments, the substrate comprises a porous material. In other embodiments, the substrate is a nonporous material. The substrate can be substantially flat or can contain wells or raised regions. The substrate can have an integral means for liquid transfer such as, for example, holes, needles, valves, pipets or combinations thereof. The substrate can also comprise a means for conducting reactions under an inert or controlled atmosphere. Thus, in one embodiment, the substrate further comprises a cover which has a means for purging the substrate and its contents with a particular atmosphere. In other

25

30

embodiments, the substrate contains means for heating or irradiating with light, sound or

ionizing radiation the materials on or within the substrate. In yet a further embodiment, the substrate comprises a means for agitating the material within or upon the substrate.

In a preferred embodiment, the substrate has a substantially flat upper surface with a plurality of indentations or wells of sufficient depth to allow a quantity of synthesis support to be contained within the indentations or wells during reaction with one or more added reagents.

The substrate is constructed of any material which can be formed into a configuration which allows for the synthesis and screening of the library of the invention. The only limitation upon the materials useful for constructing substrates is that they must be compatible with the reaction conditions to which they will be exposed. Thus, substrates useful in practicing the methods of the invention include, but are not limited to, organic and inorganic polymers, metal oxides (*e.g.*, silica, alumina), mixed metal oxides, metal halides (*e.g.*, magnesium chloride), minerals, quartz, zeolites, TEFLON, crosslinked, noncrosslinked or dendrimeric polyethylene, polypropylene, copolymers, polypropylene, polystyrene, and ceramics. Other configurations for substrates and materials from which substrates can be constructed will be apparent to those of skill in the art. Soluble catalysts can be adsorbed onto inorganic or organic substrates to form useful heterogeneous catalysts.

In an exemplary two-dimensional combinatorial library of supported organometallic compounds or catalysts, wherein a synthesis support is utilized, the following substrate synthesis support configurations are possible: i) a porous support is placed in wells wherein the reactants flow through the support from the top of the well out through a hole in the bottom of the well (or flow may be in the reverse direction); ii) a porous support is placed in wells wherein the reactants flow only into and out of the top of the well; iii) a non-porous support is placed in wells wherein the reactants flow around the substrate from the top of the well out through a hole in the bottom of the well (or flow may be in the reverse direction); iv) a non-porous support is placed in wells wherein the reactants do not flow through from top to bottom of the well, but only to and from the top of the well; or v) a non-porous or porous support that is not contained in wells wherein the reactants are deposited directly onto the substrate surface in a spatially addressable manner.

In embodiments in which a ligand or synthesis support is intended to be attached to the substrate, the substrate is functionalized to allow this attachment. In embodiments wherein the ligand is synthesized by bringing together ligand fragments on the substrate, the substrate is functionalized to allow the attachment of a first ligand
5 fragment. In embodiments wherein the ligand or synthesis support is not bound to the substrate, the substrate can be either functionalized or unfunctionalized.

Functionalizable substrates are known in the art. For example, glass plates have been functionalized to allow the conjugation of oligonucleotides thereto (*see, e.g.,* Southern, *Chem. Abstr.* 1990, 113:152979r). Another method to functionalize glass is
10 taught by Brennan, T. M., *et al.* (U.S. Patent No. 5,474,796, herein incorporated by reference), which comprises using polar silanes containing either a hydroxyl or amino group. Organic polymers are also amenable to functionalization. For instance, polypropylene can be surface derivatized by, for example, chromic acid oxidation, and subsequently converted to hydroxy- or amino-methylated surfaces which provide anchors
15 for ligands, ligand fragments or synthesis supports. Other polymers for use in practicing the instant invention include, for example, highly crosslinked polystyrene-divinylbenzene which can be surface derivatized by chloromethylation and subsequent functional group modifications. Nylon surfaces can also be derivatized as they provide an initial surface of hexylamino groups.

20 Similar to the substrate, the synthesis support can be an organic polymeric material or inorganic material including, but not limited to, alumina, silica, glass quartz, zeolites, TEFLON, *etc.* Depending on the material the synthesis support is composed of, it can be a porous, textured, or solid material, and may be flat or in the form of beads or any other geometric shape. Synthesis supports comprising, for example, functionalized
25 polystyrene, polyacrylamide and controlled pore glass are known in the art. Jones, J., "AMINO ACID AND PEPTIDE SYNTHESIS," Oxford Science Publications, Oxford, 1992; Narang, S., Ed., "SYNTHESIS AND APPLICATIONS OF DNA AND RNA," Academic Press, Inc., New York, 1987, and references therein which are herein incorporated by reference. Additionally, methods appropriate for functionalizing substrates are also appropriate for
30 functionalizing materials intended for use as synthesis supports. Once the substrate or synthesis support is functionalized, a ligand or ligand component is attached thereto.

C. Ligands

The method of the present invention is broadly applicable to all ligands which are capable of binding metal ions. The combinatorial variation of the ligand can be achieved through a solid-phase or solution-phase reaction or reactions. Alternatively, a sequence comprising a combination of solid-phase and solution-phase reactions can be used to synthesize an array of metal-binding ligands. Ligand characteristics which can be varied using the methods of the present invention include, but are not limited to, the number of coordination sites on the metal which the ligand can occupy, the charge and electronic influence of the ligand, the geometry imposed on the metal by the ligand, the geometry imposed on the ligand by the metal, *etc.* A plethora of metal-binding ligands are known in the art and other ligands and ligand parameters amenable to variation using the methods of the instant invention will be apparent to those of skill in the art. *See*, for example, Collman, J.P., *et al.* PRINCIPLES AND APPLICATIONS OF ORGANOTRANSITION METAL CHEMISTRY, University Science Books, California, 1987, and references therein which are herein incorporated by reference.

In a preferred embodiment, the general approach is: 1) synthesis of ligand libraries comprising ligands (*e.g.*, ancillary ligands) capable of stabilizing low coordination number (*e.g.*, three to five) metal alkyl complexes in a variety of geometric configurations (*e.g.*, trigonal, tetrahedral, square planar, square pyramidal, pentagonal and bipyramidal); 2) forming metal complexes of these libraries; 3) optionally reacting libraries of the metal complexes with various activators and/or modifiers; and 4) screening the resulting libraries of metal complexes for various properties and characteristics, for example, olefin polymerization activity, polymerization performance characteristics, *etc.* In an alternative embodiment, the activated metal complexes can be immobilized on a library of supports and/or linkers and then assayed for various properties (*e.g.*, olefin polymerization activity, polymerization performance characteristics). In a particularly preferred embodiment, the metal ion is a transition metal ion.

In a preferred embodiment, the ancillary ligand binds to the metal center and stabilizes it in a low coordination number and does not directly participate in the catalytic chemistry. Although lower numbers of coordination sites are typically preferred,

embodiments utilizing larger numbers of coordination sites are not precluded. When the number of coordination sites is three or greater, the metal-ligand compound can have more than one geometry.

In another preferred embodiment, the coordination sites of the ancillary ligand are 1, 2, 3 or 4, and the charge on the ligands are 0, -1, -2, -3 or -4. Other ancillary ligands include those wherein the charge is greater than the number of sites it occupies. Due to the nature of their structure, certain ligands will have more than one possible coordination number and/or more than one possible charge. For example, a ligand's charge and/or coordination number can be different when it is bound to different metals such as an early- or a late-transition metal ion. By way of further example, a ligand which is deprotonated under strongly basic conditions, *e.g.*, *n*-butyllithium, and contacted with a metal ion can have a different coordination number and/or charge than the same ligand has when reacted with a metal ion under milder conditions.

Examples of ligand, metal-ligand complexes and catalyst families which can be used in the methods of the present invention include, but are not limited to, the following:

- (1) One-site, monoanionic ancillary ligands such as $\text{Cp}^*\text{MR}_2^+\text{NCA}^-$ (wherein M represents the metal, R is an alkyl and NCA = non-coordinating anion), and mono-Cp systems in combination with methylalumoxane (MAO);
- (2) Two-site, dianionic ancillary ligands, which include, for example, bis-Cp systems (referred to in U.S. Patents Numbers 4,752,597 and 5,470,927, the teachings of which are incorporated herein by reference); mono-Cp systems where a heteroatom based ancillary ligand occupies the second site (referred to in U.S. Patent No. 5,064,802, the teachings of which are incorporated herein by reference); non-Cp, bis-amide systems (referred to in U.S. Patents Numbers 5,318,935 and 5,495,036, the teachings of which are incorporated herein by reference); and bridged bis-amido ligands and Group IV catalysts stabilized by ligands (referred to in *Organometallics* 1995, 14:3154-3156 and *J. Am. Chem. Soc.* 1996, 118:10008-10009, the teachings of which are incorporated herein by reference);

- (3) Two site, monoanionic ancillary ligands including, for example, $\text{Cp(L)CoR}^+\text{X}^-$ and related systems (referred to in WO 96/13529, the teachings of which are incorporated herein by reference);
- (4) Two site, neutral ancillary ligands, for example, the Ni^{2+} and Pd^{2+} systems. See, for example, Johnson, *et al.*, *J. Am. Chem. Soc.* 1995, 117:6414-6415 and WO 96/23010, the teachings of which are incorporated herein by reference;
- (5) Three site, neutral ancillary ligands;
- (6) Three site, monoanionic ancillary ligands;
- (7) Three site, dianionic ancillary ligands;
- (8) Three site, trianionic ancillary ligands;
- (9) Four site, neutral, monoanionic and dianionic ancillary ligands; and
- (10) Ancillary ligands where the charge is greater than the number of sites it occupies (see, for example, U.S. Patent No. 5,504,049, the teachings of which are incorporated herein by reference).

One application of the present invention is the preparation and screening of large numbers of ligands which are components of organometallic compounds or catalysts. Ligands which are used in practicing the instant invention include as part of their the binding domain of their structural motif groups such as, for example, alkyl, carbene, carbyne, cyanide, olefin, ketone, acetylene, allyl, nitrosyl, diazo, dioxo, disulfur, diseleno, sulfur monoxide, sulfur dioxide, aryl, heterocycles, acyl, carbonyl nitrogen, oxygen, sulfur, phosphine, phosphido and hydride. Additional atoms and groups comprising a metal-binding domain are known in the art and are useful in practicing the instant invention. See, for example, Collman, J.P., *et al.* PRINCIPLES AND APPLICATIONS OF ORGANOTRANSITION METAL CHEMISTRY, University Science Books, California, 1987, and references therein which are incorporated herein by reference.

As explained above, the libraries of ancillary ligands are made using combinatorial chemistry formats. Within the library, a wide range of ligand characteristics can be varied. Characteristics which are variable across the library include, for example, the ligand's bulk, electronic character, hydrophobicity/hydrophilicity, geometry, chirality, the number of coordination sites on

the metal that the ligand occupies, the charge on both the ligand core and its substituents, and the geometry the ligand imposes on the metal.

Bi-, tri- and tetra-dentate ligand systems which lend themselves to combinatorial synthesis can be constructed, for example, from the following ligand fragments which are listed according to their charge.

The synthesis of said ligand libraries can be carried out combinatorially (parallel or split pool methods) using variations of established synthetic organic methods. Neutral ligand fragments include, but are not limited to, amine (R_3N), phosphine (R_3P), arsine (R_3As), stilbines (R_3Sb), ethers (R_2O), thioethers (R_2S), selenoethers (R_2Se), teluroethers (R_2Te), ketones ($R_2C=O$), thioketones, imines ($R_2C=NR$), phosphinimine ($R_3P=NR$, $RP=NR$, $R_2C=PR$), pyridines, pyrazoles, imidazoles, furans, oxazoles, oxazolines, thiophenes, thiazoles, isoxazoles, isothrazoles, arenes, nitriles ($R-C\equiv N$), isocyanides ($R-N\equiv C$), acetylenes, olefins.

Monoanionic ligand fragments include, but are not limited to, amides (NR_2), phosphide (PR_2), silyl (SiR_3), arside (AsR_2), SbR_2 , alkoxy (OR), thiol (SR), selenol (SeR), tellurol (TeR), siloxy ($OSiR_3$), cyclopentadienyl (C_5R_5), boratobenzenes (C_5BR_6), pyrazoylborates, carboxylate (RCO_2^-), acyl (RCO), amidates, alkyl, aryl, triflates ($R_3CSO_3^-$), thiocarboxylate (RCS_2^-), halide, nitrate, and the like.

Dianionic ligand fragments include, but are not limited to, cyclooctatetrenyl ($R_8C_8^{2-}$), alkylidenes (R_2C), borylides (C_4BR_3), imido (RN), phosphido (RP), carbolide, oxide, sulfide, sulphate, carbonate, and the like.

Trianionic ligand fragments include, but are not limited to, alkylidynes ($R-C\equiv$), $-P^{3-}$ (phosphides), $-Ar$ (arsides), phosphites.

Multidentate ligands can generally be constructed by bridging ligand fragments through one or more of the pendent R-groups. Specific examples of bidentate neutral ligands [2,0] which may be constructed from the list of ligand fragments set forth above, include, but are not limited to, diimines (derived from two imine fragments), pyridylimines (derived from a pyridine and imine fragment), diamines (derived from two amine fragments), imineamines (derived from an imine and an amine), iminethioether (derived from an imine and a thioether), imineethers (derived from an imine and an ether), iminephosphines (derived from an imine and a phosphine), bisoxazoline (derived

from two oxazolines), diethers (derived from two ethers), bisphosphineimines (derived from two phosphineimines), diphosphines (derived from two phosphines) and phosphineamine (derived from a phosphine and amine). Other bidentate neutral ligand systems can be similarly constructed from the list of neutral ligand fragments set forth above.

Bidentate monoanionic ligands [2,1] can be constructed by bridging a neutral ligand fragment with a monoanionic ligand fragment from the lists set forth above. Examples include, but are not limited to, salen and other alkoxy imine ligands (derived from imine and alkoxy ligand fragments), amidoamines (derived from an amide and an amine) and amidoether (derived from an amido and ether). Other bidentate monoamine ligands can be similarly constructed.

Bidentate dianionic ligands [2,2] can be constructed either by combining two monoanionic ligand fragments or a dianionic ligand fragment and a neutral ligand fragment. Specific examples include, but are not limited to, dicyclopentadienyl ligands (derived from two cyclopentadienyl ligand fragments), cyclopentadienyl amido ligands (derived from a cyclopentadienyl and amide ligand fragments), imidothioether ligands (derived from an imido and thioether ligand fragments), imidophosphine ligands (derived from imide and phosphine ligand fragments) and alkoxyamide ligands (derived from alkoxide and amide ligand fragments). Other bidentate diamine ligands can be similarly constructed.

Bidentate ligands having charges greater than -2 can be constructed by combining monoanionic ligand fragments with di- or tri-anionic ligand fragments, or by combining two dianionic ligand fragments. Examples include bisimido ligands (derived from two imide ligands), and carbyne ether ligands (derived from carbyne and ether ligand fragments).

Tridentate neutral ligands [3,0] can be constructed by combining three neutral ligand fragments from the list set forth above. Examples include, but are not limited to, 2,5 diimino pyridyl ligands (derived from two imine and one pyridyl ligand fragments), triimidazolyl phosphines (derived from three imidazole ligand fragments bonded to a central phosphorus atom), tris pyrazoyl alkanes (derived from three pyrazole

ligands bonded to a central carbon atom). Other tridentate neutral ligands (*e.g.*, [3,1], [3,2], [3,3]) can be similarly constructed.

In preferred embodiments, the coordination numbers (CN) of the ancillary ligand are independently 1, 2, 3 or 4, and the charge on the ligands are independently 0, -1, -2, -3, or -4. The ancillary ligand or ligand fragment needn't be negatively charged, for example, positively charged ligands, such as, tropylium ($C_7H_7^+$), are also of use in practicing the present invention.

The presently preferred "families" of the coordination numbers and charges are: (i) CN = 2, charge = -2; (ii) CN = 2, charge = -1; (iii) CN = 1, charge = -1; (iv) CN = 2, charge = neutral; (v) CN = 3, charge = -1; (vi) CN = 1, charge = -2; (vii) CN = 3, charge = -2; (viii) CN = 2, charge = -3; (ix) CN = 3, charge = -3; (x) CN = 3, charge = 0; (xi) CN = 4, charge = 0; (xii) CN = 4, charge = -1; and (xiii) CN 4, charge = -2. In other preferred embodiments, the ancillary ligand has a charge which is greater than the number of coordination sites it occupies on a metal ion.

Other preferred embodiments of ligand families that lend themselves to combinatorial synthesis strategies and are depicted herein are: (1) Ancillary ligand on a support wherein, CN = 2, charge = neutral, denoted, [2,0]; (2) Ancillary ligand on a support wherein, CN = 2, charge = -1, denoted, [2,1]; (3) Ancillary ligand with metal complex on a support wherein, CN = 2, charge = -2, denoted, [2,2]; (4) Ancillary ligand off support wherein, CN = 2, charge = -1, denoted, [2,1]; (5) Ancillary ligand off support wherein, CN = 2, charge = -2, denoted, [2,2]; (6) Ancillary ligand off support with a functional linker, wherein, CN = 2, charge = -2, denoted, [2,2]; (7) Ancillary ligand off support with a "functionless" linker, wherein, CN = 2, charge = -2, denoted, [2,2]; and (8) Ancillary ligand off support wherein, CN = 3, charge = -3, denoted, [3,3].

FIG. 3 sets forth another possible route for catalyst precursor synthesis using the combinatorial synthesis approach of the present invention. In general, one can imagine other libraries of ligand cores that can be made using similar combinatorial chemistry formats. Examples include the ligand cores displayed in FIGS. 4A-G.

An important example of this invention is the placement of the acidic functionality on the R-group substituents within a library. The acidic functionality can

have profound effects on the catalytic performance of the polymerization catalyst system, including improving the ability of the catalyst to rapidly incorporate polar functional comonomers. Late transition metal catalysts, such as the Brookhart catalysts, tolerate certain polar functional comonomers; however, the rate of polymerization is greatly
5 reduced due to intramolecular coordination of the polar functionality to the metal center (see, FIG. 13A). Proper placement of an acidic moiety on the ancillary ligand would compete with the metal center for coordination of the polar functional group and accelerate the rate of polymerization by creating a vacant coordination site at the metal center as depicted in FIG. 13B. Suitable acidic functionalities include, but are not limited to, trivalent boron groups, trivalent aluminum groups, carboxylic acids and sulfuric acids.
10 The inclusion of acidic functionality on the R-groups of the ancillary ligand system is a general concept applicable to all ligand/metal complexes of this invention.

The ligands of the invention, particularly the diimine ligands, can be either symmetric or asymmetric. The symmetric ligands contain two moieties each derived
15 from identical imines. In contrast, the asymmetric ligands will contain two moieties each derived from non-identical amines. A number of synthetic routes can be used to arrive at the asymmetric ligands. For example, one carbonyl group of the diketone can be protected while the other is reacted with an amine. Following deprotection, the second carbonyl group is reacted with a second amine. Another useful reaction pathway consists
20 of adding an approximately stoichiometric amount of a first amine followed by the addition of a similar amount of a second amine. Other routes to both symmetric and asymmetric ligands will be apparent to those of skill in the art.

The R groups pendent from the ancillary core are chosen for the characteristics which they impart to the organometallic compounds. R groups affect the
25 reactivity and stability of catalysts and organometallic compounds but do not bind directly and irreversibly to the metal center. The size and electronic nature of the R groups can be varied to alter the bulk around the metal center and the electronic properties of the ligand-metal compound. R groups which are chiral can impart chirality to the ligand-metal complex. Further R groups are used to adjust the hydrophobicity/hydrophilicity of
30 the ligand-metal compound.

The R groups on the ligands are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, halogen, amino, cyano, nitro, hydroxy, alkoxy, alkylamino, acylamino, silyl, germyl, stanyl, siloxy, phosphino, aryloxy, aryloxyalkyl, substituted
5 aryloxyalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycles, substituted heterocycles, heterocyclicalkyl, substituted heterocyclicalkyl S-aryl and S-alkyl mercaptans.

The term "independently selected" is used herein to indicate that the R groups, *e.g.*, R₁, R₂ and R₃, can be identical or different (*e.g.*, R₁, R₂ and R₃ may all be
10 substituted alkyls or R₁ and R₂ may be a substituted alkyl and R₃ may be an aryl, *etc.*). Adjacent R-groups may be coupled to form cyclic structures.

A named R group will generally have the structure which is recognized in the art as corresponding to R groups having that name. For the purposes of illustration, representative R groups as enumerated above are defined herein. These definitions are
15 intended to supplement and illustrate, not preclude, the definitions known to those of skill in the art.

The term "alkyl" is used herein to refer to a branched or unbranched, saturated or unsaturated, monovalent hydrocarbon radical. When the alkyl group has from 1-6 carbon atoms, it is referred to as a "lower alkyl." Suitable alkyl radicals
20 include, for example, methyl, ethyl, n-propyl, i-propyl, 2-propenyl (or allyl), n-butyl, t-butyl, i-butyl (or 2-methylpropyl), *etc.* As used herein, the term encompasses "substituted alkyls."

"Substituted alkyl" refers to alkyl as just described including one or more functional groups such as lower alkyl, aryl, acyl, halogen (*i.e.*, alkylhalos, *e.g.*, CF₃),
25 hydroxy, amino, alkoxy, alkylamino, acylamino, acyloxy, aryloxy, aryloxyalkyl, mercapto, both saturated and unsaturated cyclic hydrocarbons, heterocycles and the like. These groups may be attached to any carbon of the alkyl moiety.

The term "aryl" is used herein to refer to an aromatic substituent which may be a single aromatic ring or multiple aromatic rings which are fused together, linked
30 covalently, or linked to a common group such as a methylene or ethylene moiety. The common linking group may also be a carbonyl as in benzophenone. The aromatic ring(s)

may include substituted or unsubstituted phenyl, naphthyl, biphenyl, diphenylmethyl and benzophenone among others.

"Substituted aryl" refers to aryl as just described including one or more functional groups such as lower alkyl, acyl, halogen, alkylhalos (*e.g.* CF_3), hydroxy, amino, alkoxy, alkylamino, acylamino, acyloxy, mercapto and both saturated and unsaturated cyclic hydrocarbons which are fused to the aromatic ring(s), linked covalently or linked to a common group such as a methylene or ethylene moiety. The linking group may also be a carbonyl such as in cyclohexyl phenyl ketone.

The term "acyl" is used to describe a ketone substituent, $-\text{C}(\text{O})\text{R}$, where R is alkyl or substituted alkyl, aryl or substituted aryl as defined herein.

The term "amino" is used herein to refer to the group $-\text{NRR}'$, where R and R' may independently be hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl or acyl. When an amino group is bonded to a metal through the nitrogen atom, it is referred to as an "amido" ligand.

The term "alkoxy" is used herein to refer to the $-\text{OR}$ group, where R is an alkyl, substituted lower alkyl, aryl, substituted aryl, wherein the substituted alkyl, aryl, and substituted aryl groups are as described herein. Suitable alkoxy radicals include, for example, methoxy, ethoxy, phenoxy, substituted phenoxy, benzyloxy, phenethyloxy, *t*-butoxy, *etc.*

As used herein, the term "mercapto" defines moieties of the general structure $\text{R}-\text{S}-\text{R}'$ wherein R and R' are the same or different and are alkyl, aryl or heterocyclic as described herein.

The term "saturated cyclic hydrocarbon" denotes groups such as the cyclopropyl, cyclobutyl, cyclopentyl, *etc.*, and substituted analogues of these structures.

The term "unsaturated cyclic hydrocarbon" is used to describe a monovalent nonaromatic group with at least one double bond, such as cyclopentene, cyclohexene, *etc.* and substituted analogues thereof.

The term "heteroaryl" as used herein refers to aromatic rings in which one or more carbon atoms of the aromatic ring(s) are substituted by a heteroatom such as nitrogen, oxygen or sulfur. Heteroaryl refers to structures which may be a single aromatic ring, multiple aromatic ring(s), or one or more aromatic rings coupled to one or

more nonaromatic ring(s). In structures having multiple rings, the rings can be fused together, linked covalently, or linked to a common group such as a methylene or ethylene moiety. The common linking group may also be a carbonyl as in phenyl pyridyl ketone. As used herein, rings such as thiophene, pyridine, isoxazole, phthalimide, pyrazole, indole, furan, *etc.* or benzo-fused analogues of these rings are defined by the term "heteroaryl."

"Heteroarylalkyl" defines a subset of "alkyl" wherein the heteroaryl group is attached through an alkyl group as defined herein.

"Substituted heteroaryl" refers to heteroaryl as just described wherein the heteroaryl nucleus is substituted with one or more functional groups such as lower alkyl, acyl, halogen, alkylhalos (*e.g.*, CF₃), hydroxy, amino, alkoxy, alkylamino, acylamino, acyloxy, mercapto, *etc.* Thus, substituted analogues of heteroaromatic rings such as thiophene, pyridine, isoxazole, phthalimide, pyrazole, indole, furan, *etc.* or benzo-fused analogues of these rings are defined by the term "substituted heteroaryl."

"Substituted heteroarylalkyl" refers to a subset of "substituted alkyls" as described above in which an alkyl group, as defined herein, links the heteroaryl group to the nucleus.

The term "heterocyclic" is used herein to describe a monovalent saturated or unsaturated nonaromatic group having a single ring or multiple condensed rings from 1-12 carbon atoms and from 1-4 heteroatoms selected from nitrogen, phosphorous sulfur or oxygen within the ring. Such heterocycles are, for example, tetrahydrofuran, morpholine, piperidine, pyrrolidine, *etc.*

The term "substituted heterocyclic" as used herein describes a subset of "heterocyclics" wherein the heterocycle nucleus is substituted with one or more functional groups such as alkyl, acyl, halogen, alkylhalos (*e.g.*, CF₃), hydroxy, amino, alkoxy, alkylamino, acylamino, acyloxy, mercapto, *etc.*

The term "heterocyclicalkyl" defines a subset of "alkyls" wherein an alkyl group, as defined herein, links the heterocyclic group to the nucleus.

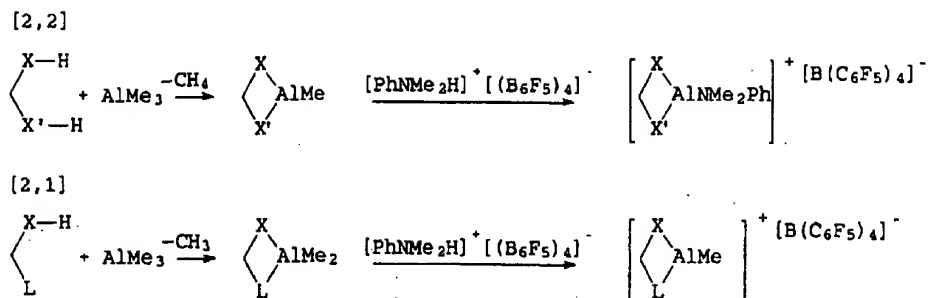
The term "substituted heterocyclicalkyl" defines a subset of "heterocyclic alkyl" wherein the heterocyclic nucleus is substituted with one or more functional groups

such as lower alkyl, acyl, halogen, alkylhalos (*e.g.*, CF₃), hydroxy, amino, alkoxy, alkylamino, acylamino, acyloxy, mercapto, *etc.*

In a preferred embodiment, an array of ligand moieties is synthesized on a substrate. This array is a combinatorial array of spatially separated substrate- or synthesis support-bound ligand moieties. Any of the previously discussed ligand types are
5 amenable to this synthesis strategy; however, in a preferred embodiment, the array of ligand moieties comprises neutral bidentate ligands or chelating diimine ligands. Following its synthesis, the array of ligand moieties can be bound to a metal ion (*e.g.*, transition metal ion, main group metal ion, and lanthanide ions).

In another preferred embodiment of this invention, a metal-ligand array or library is prepared such that each member of the ligand array is contacted with a metal ion precursor in the presence of a suitable solvent, wherein the metal-ligand array comprises neutral bidentate ligand moieties and the metal precursor is stabilized by at least one labile neutral Lewis base. Transition metal ion precursors are particularly
10 preferred. In another preferred embodiment, the ligand moieties are diimine ligands and the transition metal precursor is selected from a Group 10 transition metal. In yet another preferred embodiment, the ligands are monoanionic bidentate ligand moieties and the transition metal precursor is stabilized by at least one labile anionic leaving group ligand.

In a preferred embodiment of this invention, ligand libraries described
20 herein can be reacted with main group metal precursors to produce catalyst libraries. Such catalyst libraries are used for a variety of organic transformations requiring Lewis acidic sites, including stereo-selective coupling reactions (where a chiral Lewis acid is required), olefin oligomerization and olefin polymerization. As example of such reactions involves the reaction of trialkylaluminum with [2,2] or [2,1] ligand libraries, wherein
25 each member of the ligand library is in the di- or mono-protic form respectively. This reaction will produce organometallic libraries comprising bidentate ligands bound to mono- or di-alkylaluminum centers. Such libraries can further be modified by reaction with an ion-exchange activator, such as [PhNMe₂H]⁺[B(C₆F₅)₄]⁻, to produce ligand-stabilized cationic aluminum reagents that are capable of acting as catalysts for
30 organic coupling reactions, olefin oligomerization, and olefin polymerization. Examples of such [2,2] and [2,1] reactions are displayed below in Scheme 1:

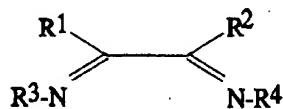


Scheme 1

These compounds are useful as catalysts in, for example, the polymerization of organic monomers. Organic monomers include, but are not limited to, ethylene, propylene, butene, isobutylene, hexene, methylacrylate, methyl vinyl ether, dienes, *etc.* Reactions can be carried out in gas phase or in solution, either on or off the substrate or synthesis support. The ability to assay catalytic properties of a metal-ligand compound on the substrate or synthesis support allows one to make libraries of catalysts bound to a variety of substrates or synthesis supports such as polystyrenes, silica, alumina, *etc.*

In still another preferred embodiment of this invention, a polymer blend is produced such that at least two members of the metal-ligand libraries are contacted with at least one cocatalyst and at least one monomer. In yet another preferred embodiment, olefins, diolefins and acetylenically unsaturated monomers are polymerized such that at least two members of the metal-ligand library are contacted with at least one cocatalyst and with at least one monomer.

Another exemplary library comprises diimine ligands of the general formula set forth below (I). These libraries can be synthesized by solution- or solid-phase methodologies or a combination thereof.

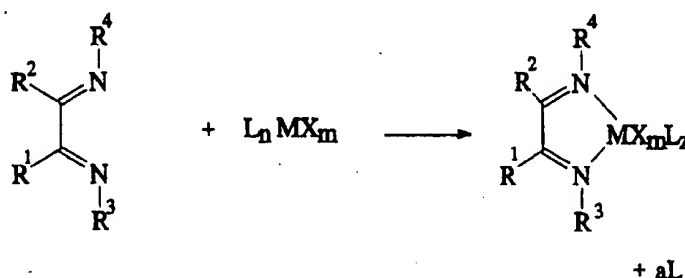


(I)

Substituent groups R^1 , R^2 , R^3 and R^4 can be chosen from a wide variety of organic fragments as discussed above. The role of the R group substituent is to modify the steric, stereochemical, solubility and electronic properties of the ligand system. The R group can be polar or nonpolar, and comprise neutral, acidic or basic functionalities.

Suitable R groups include those described above and also organometalloid radicals, such as, for example, silyl or germyl radicals. The molecular weight of the R group substituent will, in general, range from 1 to 10,000 daltons. Polymeric or oligomeric R groups having molecular weights greater than 10,000 can also be prepared.

The diimine ligand libraries described above can be contacted with a variety of metallic precursors to form organometallic libraries. In one method, the ligand library is contacted with a coordinatively unsaturated metallic precursor or a metallic precursor complexed by a weakly bound leaving group ligand as depicted below in Scheme 2.



Scheme 2

wherein:

L is a neutral Lewis base, n is an integer greater than or equal to zero;

z is an integer greater than or equal zero;

"a" represents the number of displaced L groups, and $a + z = n$;

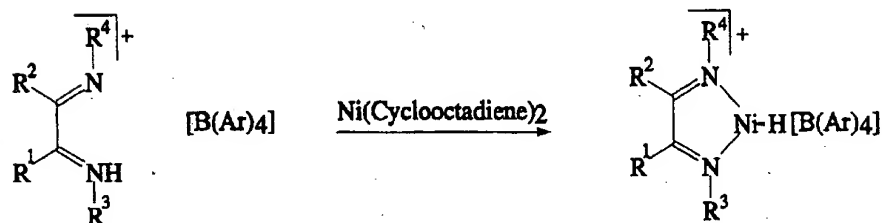
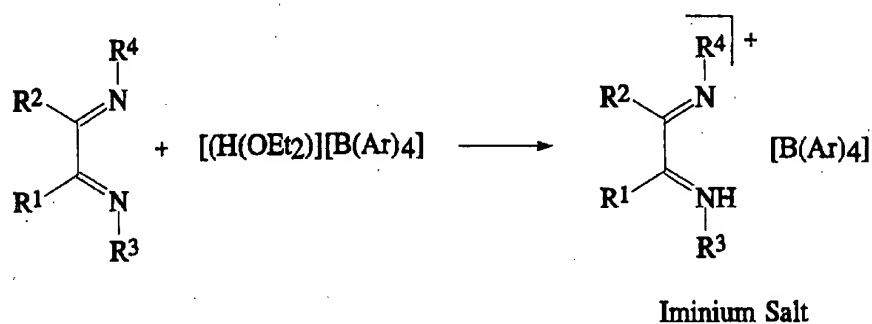
M is a metal;

X is an anionic ligand such as halide, hydrocarbyl or hydride; and

m represents the number of X ligands, and is an integer greater than or equal to zero.

Metal catalysts comprising non-coordinating anions can be synthesized by contacting a low valent metal precursor with the protonated form of a ligand library. For

example, diimine stabilized transition metal catalysts can be prepared by a two step procedure comprising: 1) reacting the diimine library with the Bronsted acid of a non-coordinating anion to form an iminium salt library, and 2) contacting the iminium salt library with a suitable low valent metallic precursor. An example of such a process is depicted below in Scheme 3.



Scheme 3

In certain embodiments, the ligands of the invention are made as pure stereo-, regio- or conformational isomers or, alternatively, the ligands can be a mixture of isomers. Metals suitable for use in the present invention include, but are not limited to, Cr, Mo, W, Pd, Ni, Pt, Ir, Rh, Co, *etc.* Activators suitable for use in the methods of the present invention include, but are not limited to, MAO, $[\text{H}(\text{OEt}_2)]^+[\text{BAr}_4]^-$, *etc.*

Solvents suitable for use in the methods of the present invention include, but are not limited to, hexane, CH_2Cl_2 , toluene, CHCl_3 , *etc.*

The techniques described above are used to synthesize more than 3, more than 10, more than 20, more than 50, more than 100, more than 200, more than 500, more than 1,000, more than 10,000, more than 100,000 different compounds. Chemical synthesis steps can be conducted with a combination of solid-phase and solution-phase steps on substrates or synthesis supports such as pins, beads, or in wells. The methodology for varying ligands can be performed through either the parallel dispensing of reagents to spatially addressable sites, or by known "split-and-pool" combinatorial methodology.

The methods of the present invention also encompass embodiments wherein the linkage between the ligand and the substrate or synthesis support is varied in length and/or chemical composition.

D. Linkers

Combinatorial libraries can also be used to identify the optimal attachment of an organometallic catalyst to a substrate or solid support (*e.g.*, silica, alumina, polystyrene, *etc.*). In another embodiment of the present invention, linker groups are interposed between the substrate and the ligand and/or the synthesis support and the ligand and/or the substrate and the synthesis support. A wide variety of cleavable and noncleavable linker groups are known to and used by those of skill in the various chemical arts and can be used in the present invention to assemble ligand and organometallic libraries. The length and structure of the linkers are potential variables which can affect catalyst performance and can be an element of library design. Examples of linkers suitable for use in the methods of the present invention are described in greater detail in PCT US94/05597, the teachings of which are incorporated herein by reference.

E. Metals

Once formed, the ligand libraries of the present invention can be contacted with metal ions to produce organometallic compounds. These compounds are typically

catalysts. The metal ions are in the form of simple salts, mixed salts or organometallic compounds.

When the methods of the invention are used to discover an active catalyst, all classes of metal ions can be used. Broad classes of metal ions for use in practicing the instant invention include, but are not limited to, transition metal ions, lanthanide ions,
5 main group metals, and actinide ions.

F. Immobilized Reagents

In practicing the instant invention to produce combinatorial solution libraries it is useful to use one or more immobilized reagents which accomplish different
10 tasks. Thus, encompassed within the present invention is the use of, for example, immobilized bases, acids, proton sponges, oxidants, reductants, acylation and alkylation catalysts and the like. Many such immobilized agents are known to and used by those of skill in the art.

G. Non-coordinating Anions (NCA)

15 The presence, in a catalyst, of anions which are non- or weakly-coordinated to the metal center is known in the art to yield enhanced catalyst reactivity compared to those catalysts in which the anion is coordinated to the metal center (*See*, for example, U.S. Patent Nos. 5,198,401; 5,278,119; 5,502,017 and 5,447,895, the complete disclosures of which are incorporated by reference herein).

20 Anions which are bulky, highly stable and non-coordinating to the cationic metal center and which exhibit strong Lewis acidity and high reactivity are of particular utility in practicing the present invention. In preferred embodiments, the non-coordinating anions are boron-containing structures. In more preferred embodiments, the non-coordinating anions are boron tetraaryl structures in which the four aryl structures are
25 substituted with one or more electron withdrawing substituents (*e.g.*, fluorine) and at least one bulky R group to increase the solubility and the thermal stability of the organometallic or catalyst system. Representative R groups are as discussed above in the context of ligands. In preferred embodiments, the R groups are C₁ to C₂₀ alkyl or C₁ to C₂₀ alkyl-substituted group 14-metalloids (*e.g.*, silicon, germanium or tin). Other non-

coordinating ions of use in practicing the present invention will be apparent to those of skill in the art.

H. Diimine Catalyst Library Design and Synthesis

Having broadly set forth the principles and methods for the combinatorial
5 synthesis of arrays of ligands and organometallic compounds, the design and synthetic methodologies for creating solution and solid phase libraries of diimine ligands and organometallic complexes will now be described.

FIG. 14 illustrates the design of a 96-well ligand and ligand-metal solid-
phase library using Merrifield resin and the chemistry described in the Examples section.
10 The library is composed of 48 diimine ligands derived from a Merrifield Resin-bound diketone precursor and 48 substituted anilines. The Merrifield Resin-bound diketone precursor is added to each of the 96-wells in the microtiter plate. An excess of each aniline is added to two of the wells within the microtiter plate, and the reactions are carried out and worked up using the protocols described in the Examples section. Ni and
15 Pd metal ion precursors are combined with each resulting resin-bound diimine to produce the desired catalyst precursor. The catalyst precursors can be activated using appropriate activators and screened for activity and performance using the techniques described in the present invention.

Solution-phase diimine ligand and catalyst libraries can also be prepared
20 using the methods of this invention. Solution-phase combinatorial chemistry is greatly facilitated by the use of solid-phase reagents which either catalyze reactions, deliver reagents or adsorb byproducts and/or unreacted starting materials. The general approach as it relates to the parallel synthesis of diimine ligands and the corresponding metallic complexes is displayed in FIG. 15 and described in Section 1.1 of the Examples section.
25 Variation of the ligand backbone substitution (*i.e.*, R₁ and R₂) can be accomplished by utilizing a large variety of commercially-available 1,2-diketones, examples of which are illustrated in FIG. 16. The solution-phase imine condensation can be catalyzed by, for example, a variety of solid-phase immobilized Lewis-acid catalysts/dehydrants (FIG. 17). Examples include:

[PS]-CH₂-O-TiCl₃;
[PS]-CH₂-O-AlCl₂;
[PS]-SO₂-O-TiCl₃;
[PS]-SO₂-O-AlCl₂;
5 [PS-PEG]-TiCl₄;
[PS-PEG]-AlCl₃;
[SiO₂]-O-TiCl_n; and
[SiO₂]-O-AlCl_n.

10 In one embodiment, these catalysts are employed in conjunction with a solid-phase proton scavenging reagent such as [PS]-CH₂-piperidine.

Selective scavenging of excess aniline in the presence of diimines can be accomplished with a variety of solid-phase reagents. Examples include:

[PS]-C(O)Cl + [PS]-CH₂-piperidine;
[PS]-SO₂Cl + [PS]-CH₂-piperidine;
15 [PS]-NCO; and
[PS]-NCS.

III. SCREENING OF COMBINATORIAL LIBRARIES

The success of combinatorial chemistry depends upon the ability to first synthesize collections (libraries) of molecular compounds (members) where each member
20 has a unique elemental composition, and second, to rapidly characterize each member to identify compounds having specific, desired properties. Accordingly, in a preferred embodiment, the array of materials is synthesized on a single substrate. By synthesizing the array of materials on a single substrate, screening the array for materials having useful properties is more easily carried out.

25 As such, following the synthesis of the library, the library of compounds is screened for a useful property. Properties which can be screened for include, for example, electrical, thermal mechanical, morphological, optical, magnetic, chemical, *etc.* In a preferred embodiment, the useful property is a property relating to a polymerization reaction. In another preferred embodiment, the useful property is a mechanical property,
30 an optical property, a physical property or a morphological property. In certain preferred

embodiments, the useful property is a chemical property such as, for example, the lifetime of the metal-ligand compounds, the stability of these compounds under specific reaction conditions, the selectivity of the library compounds for a particular reaction, the conversion efficiency of the library compounds in a particular reaction or the activity of the library compounds in a particular reaction. Other properties which can be screened for are set forth in Table I, *infra*. Any material found to possess a useful property can subsequently be prepared on a large-scale. In the interest of simplicity, the analytical methods of the present invention are generally exemplified by reference to their use with libraries of catalytic compounds. Such use is not intended to limit the scope of the analytical methods which are also applicable to the analysis of libraries of organometallic compounds.

TABLE I. EXAMPLES OF PROPERTIES WHICH CAN BE SCREENED FOR

ELECTRICAL:	SUPERCONDUCTIVITY
	CRITICAL CURRENT
	CRITICAL MAGNETIC FIELD
	CONDUCTIVITY
	RESISTIVITY FOR RESISTIVE FILMS
	DIELECTRIC CONSTANT
	DIELECTRIC STRENGTH
	DIELECTRIC LOSS
	STABILITY UNDER BIAS
	POLARIZATION
	PERMITTIVITY
	PIEZOELECTRICITY
	ELECTROMIGRATION
THERMAL:	COEFFICIENT OF EXPANSION
	THERMAL CONDUCTIVITY
	TEMPERATURE VARIATION
	VOLATILITY & VAPOR PRESSURE
MECHANICAL:	STRESS
	ANISOTROPY
	ADHESION
	HARDNESS
	DENSITY
	DUCTILITY
	ELASTICITY
	POROSITY
MORPHOLOGY:	CRYSTALLINE OR AMORPHOUS
	MICROSTRUCTURE
	SURFACE TOPOGRAPHY
	CRYSTALLITE ORIENTATION
OPTICAL:	REFRACTIVE INDEX

	ABSORPTION
	BIREFRINGENCE
	SPECTRAL CHARACTERISTICS
	DISPERSION
	FREQUENCY MODULATION
	EMISSION
MAGNETIC:	SATURATION FLUX DENSITY
	MAGNETORESISTANCE
	MAGNETORESTRICTION
	COERCIVE FORCE
MAGNETIC:	PERMEABILITY
CHEMICAL:	COMPOSITION
	COMPLEXATION
	ACIDITY-BASICITY
	CATALYSIS
	IMPURITIES
	REACTIVITY WITH SUBSTRATE
	CORROSION & EROSION RESISTANCE

The properties listed in Table I can be screened for using a wide range of
 5 methods and devices known to and used by those of skill in the art. Such methods
 include, but are not limited to, from the group consisting of scanned mass spectrometry,
 chromatography, ultraviolet imaging, visible imaging, infrared imaging, electromagnetic
 imaging, ultraviolet spectroscopy, visible spectroscopy, infrared spectroscopy,
 electromagnetic spectroscopy and acoustical methods. In addition, scanning systems
 10 which can be used to screen for the properties set forth in Table I include, but are not
 limited to, the following: scanning Raman spectroscopy; scanning NMR spectroscopy;
 scanning probe spectroscopy including, for example, surface potentialometry, tunnelling
 current, atomic force, acoustic microscopy, shearing-stress microscopy, ultra fast photo
 excitation, electrostatic force microscope, tunneling induced photo emission microscope,
 15 magnetic force microscope, microwave field-induced surface harmonic generation

microscope, nonlinear alternating-current tunnelling microscopy, near-field scanning optical microscopy, inelastic electron tunneling spectrometer, *etc.*; optical microscopy in different wavelength; scanning optical ellipsometry (for measuring dielectric constant and multilayer film thickness); scanning Eddy-current microscope; electron (diffraction) microscope, *etc.*

In a presently preferred embodiment, a scanning detection system is employed. In one embodiment, the substrate having an array of materials thereon is fixed and the detector has X-Y motion. In this embodiment, the substrate is placed inside a sealed chamber, close to the detector. The detector (*e.g.*, an RF Resonator, a SQUID detector, *etc.*) is attached to a rigid rod with low thermal conductivity coupled to an X-Y positioning table at room temperature with a scanning range of up to 1 inch and a 2 μm spatial resolution. The position of the detector is controlled using stepping motors (or servomotors) connected to a computer-controlled positioner. In another embodiment, the detector is fixed and the substrate having an array of materials thereon has R- θ motion. In this embodiment, the substrate is placed on a rotating stage (*e.g.*, a spur gear) driven by a gear rack which is coupled to a micrometer and a stepping motor. In each of these embodiments, the temperature of the detector and the substrate can be lowered by, for example, helium exchange gas. This scanning system can be operated at temperatures ranging from 600°K down to 4.2°K (when immersed in liquid helium).

The use of combinatorial chemistry for discovering and optimizing new catalysts, is enhanced by the use of high throughput methods for measuring such properties as activity (*i.e.*, turnover, selectivity in converting reactants into desired products, and stability during operation under a wide variety of substrate concentrations and reaction conditions). Spatially selective characterization methods include those capable of: (i) Identification and characterization of gas phase products and volatile components of the condensed phase products; (ii) Identification and characterization of condensed phase products; and (iii) Measurement of physical properties of the catalyst elements on the library.

The high throughput (0.1 to greater than 1000 library elements per second), position sensitive (resolution 0.01 - 10 mm), methods described herein, include several fundamentally different approaches including scanned mass spectrometry and

chromatography, ultraviolet, visible, infrared, and other electromagnetic imaging and spectroscopy, and acoustic methods. Methods for measuring catalytic activity and specificity may involve, for example, direct measurement of product concentrations or indirect measurement of the heat of reaction. Parallel screening methods have the common approach of integrating position sensitive photon detectors into the measurement system while the serial methods rely on controlled scanning of the library or detector/source relative to one another.

The activity of each of the compounds within an array is measured using one or more of several optical, thermal, or mass spectral techniques. In one implementation, the fact that the exothermic or endothermic nature of a reaction will translate into temperature differences localized to the area adjacent to a compound, is used to identify in parallel the active sites within an array of compounds by monitoring that change in temperature with infrared imaging techniques. The same technique can also be used to quantify in parallel the stability of each catalyst with an array of compounds. By measuring the decay of activity over time for each site within the array, the lifetime of the catalysts can be quantified.

Selectivity measurements within a combinatorial array of catalysts are measured using techniques such as ultraviolet/visible/infrared imaging and/or spectroscopy, chromatography, or mass spectrometry. One of the most general methods of the present invention is the use of a scanning mass spectrometry to locally measure the relative concentrations of reactants and products in close proximity to a catalyst compound on the library. Such a system can be enhanced using laser desorption techniques which vaporize liquid, bound reactants and/or products in a spatially localized format and facilitate the intake of chemicals in the scanning mass spectrometry measurement system.

Optical methods are used for activity and selectivity characterization. Infrared spectroscopy or spectroscopic imaging is used to monitor the relative concentration of end groups, and saturated backbone monomer units along a polymer chain on a polymer. In this manner, the average molecular weight and average composition of a copolymer in a library element can be estimated. UV/visible spectroscopic techniques are used, for example, in the analysis of reactions involving

compounds with a suitable chromophore (e.g., aromatic and unsaturated compounds). Another example is the partial oxidation of benzene into phenol which leads to different electronic absorption spectra for the product. In this case, benzene provides a distinct spectroscopic fingerprint from phenol, and, thus, the relative amounts of each compound can be measured using UV/visible spectroscopy.

Rapid chromatographic analysis of reactants and products, either as separate entities or mixtures, are used to assay in parallel product conversion, product identity, isomeric purity, *etc.* Also, flow rates through vertical tubes of product polymer solutions are used to gauge the viscosity and hence the molecular weight of the polymer when polymerization reactions are effected. In addition, mass spectroscopy can be used for gas phase characterization.

In addition to the foregoing, those of skill in the art will readily appreciate that numerous other methods and devices can be used to screen the libraries of compounds for useful properties. Such methods and devices are within the scope of the present invention.

The present invention is directed to the synthesis of supported and unsupported ligand molecules and their subsequent conversion to organometallic and catalyst compounds. In the examples which follow, the synthesis of two representative classes of ligands, diimines and pyridylimines, using the methods of the invention are detailed. Representative examples using both solution- and solid-phase methodologies are provided. The use of these two broad ligand classes to further describe the invention is intended to be exemplary and is not intended to define or limit the scope of the invention or of the ligands, organometallic compounds or catalysts which can be assembled using the methods of the instant invention.

IV. EXAMPLES

The following examples illustrate a variety of embodiments of the present invention. Example 1 illustrates the solution-phase synthesis of bis-imine ligands. Example 2 illustrates the concept of solid phase combinatorial synthesis of diimine ligands. Example 3 illustrates the application of the methods of the present invention to the solid phase synthesis of diimine ligands, wherein the diimine is synthesized on the

support. Example 4 illustrates the utility of the catalysts of the present invention in polymerizing olefins. Both the supported and unsupported catalysts of the invention were assayed for their ability to polymerize ethylene to poly(ethylene). The polymerization of higher olefins such as hexene was also examined. Example 5 details the preparation of a pyridyl imine ligand and its nickel complex. The catalyst was used to polymerize both hexene and ethylene. Example 6 illustrates reaction schemes which can be used to prepare a variety of [2,0], [2,1], and [2,2] ligand libraries. Such [2,0], [2,1], and [2,2] ligand libraries can be prepared using solution or solid phase methodologies from a salen-based scaffold.

EXAMPLE 1

Example 1 details the solution-phase synthesis of bis-imine ligand components of a combinatorial library of ligands. General strategies were developed for aryl bis-imines with both electron-donating and electron-withdrawing groups on the aryl moiety.

1.1 Synthesis of [(2,4,6-Me₃Ph)DABMe₂]NiBr₂ Through Solution-Phase Methodology

a. Synthesis of Resin-Bound Lewis-Acid Catalyst PS-CH₂-O-TiCl₃

To 10 g hydroxymethylpolystyrene (1.12 mmol OH/g resin) swollen in 100 mL of anhy. CH₂Cl₂ was added 4.24 g (2.24 mmol) TiCl₄, and this suspension was heated to reflux under N₂ with gentle stirring for 1 h. The resin was filtered under N₂, washed with 5 x 50 mL anhy. CH₂Cl₂ and then dried under high vacuum for 24 h. Chloride analysis (9.98%) provided a loading of 0.94 mmol TiCl₃/g resin.

b. Synthesis of Aniline Scavenging Reagent PS-SO₂Cl

To 10 g of PS-SO₂-OH (Amberlyst 15, washed with MeOH and dried in vacuo; ca. 5 mmol OH/g resin) in 50 mL of anhy. CH₂Cl₂ was added 3 g (25 mmol) of SOCl₂. This mixture was heated at reflux under N₂ for 18 h. The resin was filtered

under N₂, washed with 5 x 50 mL of anhy. CH₂Cl₂, then dried under high vacuum for 24 h. Chloride analysis (16.05%) provided a loading of 4.53 mmol SO₂Cl/g resin.

c. Ligand Synthesis

To a suspension of 250 mg (0.24 mmol) of PS-CH₂-OTiCl₃ and 93 mg (0.25 mmol) PS-CH₂-piperidine in 5 mL of anhy. CH₂Cl₂ was added 676 mg (0.5 mmol) of 2,4,6-trimethylaniline followed by 8.6 mg (0.1 mmol) 2,3-butanedione. This mixture was shaken at RT for 24 h. then filtered and washed with 2 x 1 mL anhy. CH₂Cl₂. GC analysis showed 2,4,6-trimethylaniline and the product (2,4,6-Me₃Ph)DABMe₂ in an approximately 3:1 ratio.

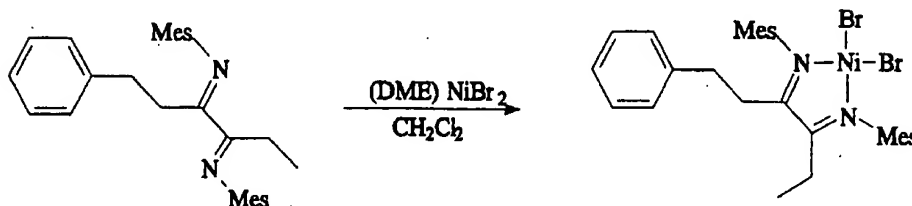
10 d. Excess Aniline Scavenging

To the 3:1 mixture of 2,4,6-trimethylaniline and (2,4,6-Me₃Ph)DABMe₂ was added 111 mg of PS-SO₂Cl and 185 mg of PS-CH₂-piperidine and this mixture shaken at RT for 12 h. The resin was filtered and washed with 2 x 0.5 mL CH₂Cl₂. The filtrate was evaporated to provide 285 mg (89%) of (2,4,6-Me₃Ph)DABMe₂ as yellow
15 crystals.

e. Synthesis of [(2,4,6-Me₃Ph)DABMe₂]NiBr₂ Complex

A suspension of 285 mg (0.89 mmol) of (2,4,6-Me₃Ph)DABMe₂ and 274 mg (0.89 mmol) (DME)NiBr₂ in 5 mL CH₂Cl₂ was shaken in a sonication bath at RT for 24 h. The resultant solid was collected by filtration and washed with 3 x 1 mL CH₂Cl₂ to
20 provide 456 mg (95%) [(2,4,6-Me₃Ph)DABMe₂]NiBr₂ as a red powder.

1.2 Preparation of (2,4,6-Me)₂DAB(Me)EtPh Nickel (II) Dibromide



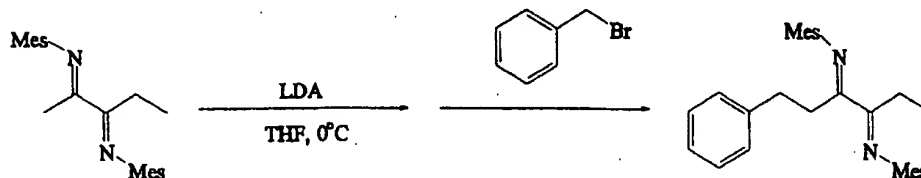
Scheme 4

(2,4,6-Me)₂DAB(Me)EtPh (0.50 g, 1.17 mmol) and (DME)NiBr₂ (0.36 g, 1.17 mmol) were dissolved in 8 ml dry CH₂Cl₂ under nitrogen and stirred at room temperature for 8 hr. The resulting reddish-brown solution was concentrated and the remaining residue was recrystallized from CH₂Cl₂/hexane to afford 0.40 g of (2,4,6-Me)₂DAB(Me)EtPh nickel (II) dibromide as reddish-brown crystals in 53% yield. Anal. Calcd for C₃₀H₃₆N₂NiBr₂: C 55.88; H 5.62; N 4.34. Found: C 55.08; H 5.55; N 4.21.

1.3 Solution-Phase Synthesis (Spectroscopic model compounds)

Compounds with all of the structural features of the immobilized compounds are prepared in tandem with the immobilized compounds. The model compounds allowed the proper spectroscopic parameters to be determined for the immobilized analogues. Additionally, these compounds have a catalytic activity which is similar to that exhibited by the analogous immobilized metal-ligand compounds.

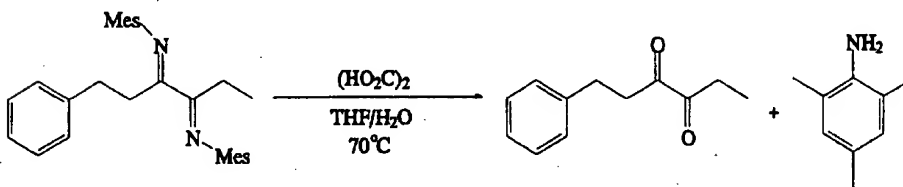
1.3(a) Alkylation of (2,4,6-Me)₂DAB(Me)Et with Benzyl Bromide



Scheme 5

To a cooled solution (0°C) of (2,4,6-Me)₂DAB(Me)Et (2.00 g, 5.99 mmol) in 15 ml dry THF under nitrogen was added LDA (4.40 ml, 6.59 mmol, 1.5 M in THF). After stirring at 0°C for 2 hr, benzyl bromide (0.86 ml, 7.19 mmol) was added and the resulting solution was stirred 3 hr at 0°C and 10 hr at room temperature. The reaction mixture was concentrated on a rotovap and the remaining oily residue was taken up in 50 ml Et₂O and washed with H₂O (2 x 50 ml). The Et₂O layer was dried over MgSO₄, filtered and concentrated. The crude material was passed through a plug of silica gel with CH₂Cl₂ and concentrated once more to afford 2.54 g of the desired product in 95% yield as a yellow oil. ¹H NMR 300 MHz, (CDCl₃) δ 7.23-7.28 (m, 3H), 7.19 (d, 2H, J = 6.9 Hz), 6.98 (s, 2H), 6.94 (s, 2H), 2.87 (br s, 4H), 2.64 (q, 2H, J = 7.6 Hz), 2.37 (s, 3H), 2.35 (s, 3H), 2.14 (s, 6H), 2.06 (s, 6H), 1.12 (t, 3H, J = 7.6 Hz); ¹³C NMR 75 MHz, (CDCl₃) δ 171.97, 169.97, 145.85, 145.56, 141.15, 132.28, 132.20, 128.66, 128.28, 128.15, 125.97, 124.37, 32.76, 31.28, 22.24, 20.67, 18.22, 18.06, 11.24; IR (C=N) @ 1635 cm⁻¹.

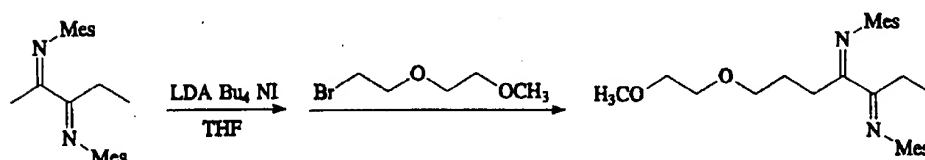
1.3(b) Hydrolysis of Benzyl (2,4,6-Me)₂DAB(Me)Et (Methyl)



Scheme 6

A stirring solution of benzyl (2,4,6-Me)₂DAB(Me)Et (0.20 g, 0.47 mmol) and oxalic acid (0.20 g, 2.35 mmol) in 10 ml THF/H₂O (5:1 v/v) was heated to 70°C for 8 hr. After cooling to room temperature and diluting with 30 ml Et₂O, the organic layer was washed with H₂O (2 x 10 ml), dried over MgSO₄, filtered and concentrated. GC/MS analysis revealed 1-phenyl-3,4-hexanedione and 2,4,6-trimethylaniline as the only detectable species in the crude reaction mixture. Pure 1-phenyl-3,4-hexanedione (89 mg) was obtained by passing the crude mixture through a plug of silica gel in > 95% yield as

5



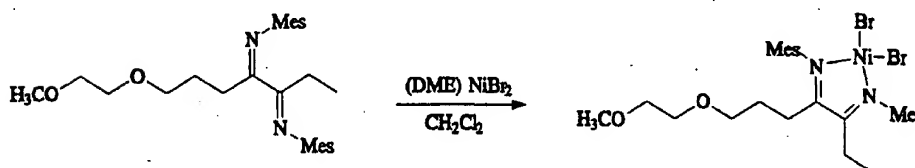
Scheme 7

10

15

20

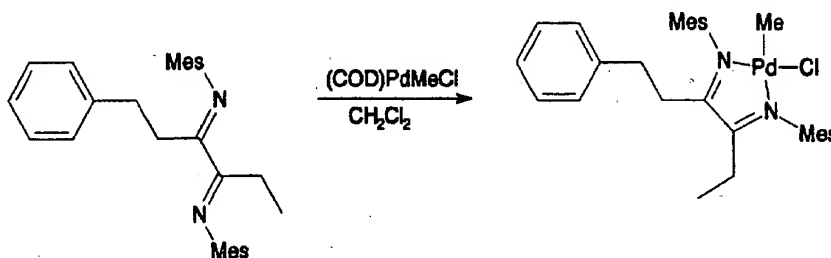
1.3(d) Preparation of (2,4,6-Me)₂DAB(1-Methoxyethoxyethyl)Et Nickel (II) Dibromide



Scheme 8

- 5 (2,4,6-Me)₂DAB(1-methoxyethylpropyloxy) ethane (0.29 g, 0.67 mmol) and (DME) NiBr₂ (0.21 g, 0.67 mmol) were taken up in 6 ml dry CH₂Cl₂ under nitrogen and stirred at room temperature for 24 hours. The reaction mixture was filtered through celite and concentrated to afford crude (2,4,6-Me)₂DAB(1-methoxyethoxypropyl)ethyl nickel (II) dibromide which was purified through recrystallization from CH₂Cl₂/hexane to afford 0.35 g of pure product as a reddish-brown solid in 80% yield. Anal. Cald for C₂₈H₄₀N₂O₂NiBr₂: C 51.33; H 6.15; N 4.27. Found: C 52.01; H 6.26; N 3.91.
- 10

1.3(e) Preparation of (2,4,6-Me)₂DAB(Me)EtPh Palladium (II) (Me)Cl



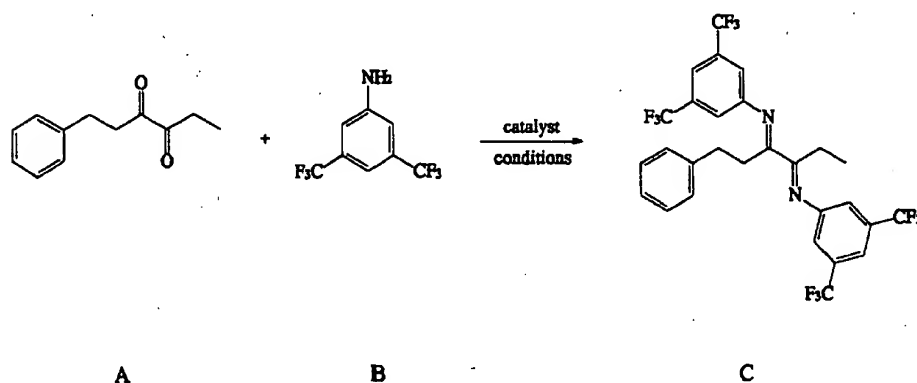
Scheme 9

- 15 (2,4,6-Me)₂DAB(Me)EtPh (0.23 g, 0.65 mmol) and (COD)PdMeCl (0.17 g, 0.65 mmol) were dissolved in 8 ml dry CH₂Cl₂ under nitrogen and stirred at room temperature for 8 hr. The resulting orange-red solution was concentrated and the remaining residue was recrystallized from CH₂Cl₂/hexane to afford 0.30 g of

(2,4,6-Me)₂DAB(Me)EtPh palladium (II) (Me)Cl as a orange solid in 80% yield. Anal. Cald for C₃₁H₃₉N₂PdCl: C 64.02; H 6.76; N 4.81. Found: C 63.47; H 6.70; N 4.62.

1.4 Solution-Phase Combinatorial Synthesis

5 Catalytic bis-imine formation generally works well for aniline derivatives containing electron donating groups (X = EDG). However, anilines containing electron withdrawing groups (X = EWG) are much less nucleophilic and bis-imine formation is not observed under standard conditions (Entry 1, Table 1). Therefore, conditions were sought to initiate bis-imine formation with a representative electron deficient aniline derivative (X = 3,5-CF₃). The general scheme is displayed in Scheme 10. These results are summarized in Table 1.



Scheme 10

TABLE 1

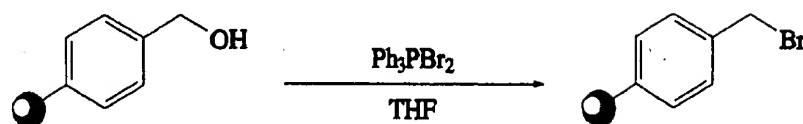
Entry	A Equiv.	B Equiv.	Catalyst (Equiv.)	Conditions	C Yield (GC/MS)
1	1	20	HCO ₂ H (10)	CH ₂ Cl ₂ /MeOH RT, 12 hr.	0%
2	1	20	H ₂ SO ₄ (10)	CH ₂ Cl ₂ /MeOH RT, 12 hr.	20%
3	1	20	(CO ₂ H) ₂ (10)	CH ₂ Cl ₂ /MeOH RT, 12 hr.	65%
4	1	10	(CO ₂ H) ₂ (10)	(CH ₃ O)CH 70°C, 12 hr.	0%
5	1	20	(CO ₂ H) ₂ (10)	Si(OEt) ₄ RT, 12 hr.	60%
6	1	13	TiCl ₄ (2)	CH ₂ Cl ₂ RT, 12 hr.	80%
7	1	15	TiCl ₄ (5)	CH ₂ Cl ₂ RT, 12 hr.	95%

EXAMPLE 2

Example 2 illustrates the concept of solid phase combinatorial synthesis of diimine ligands. Through the approach outlined below, alkylation of a diimine ligand with 1 % cross-linked (bromomethyl)polystyrene is carried out. The supported diimine is hydrolyzed to give the corresponding resin bound diketone which serves as starting material for synthesizing a broad range of chemically diverse bis-imine ligands. The analogous solution-phase reactions are performed in parallel and are fully characterized spectroscopically and serve to provide spectroscopic handles (¹H and ¹³C NMR, FTIR, Raman IR) to help facilitate the characterization of the desired resin bound compounds.

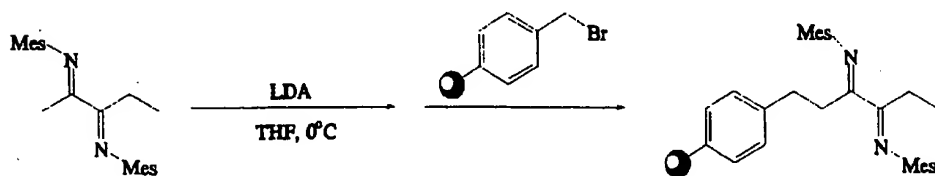
2.1 Solid Phase Combinatorial Strategy

This approach involves the parallel synthesis of organometallic libraries immobilized on a polymer support. Advantages to this approach include exposing a large excess of the reagents to immobilized substrates and effectively driving reactions to completion. Excess reagents and/or side products are then removed from the desired immobilized substrate by filtration followed by extensive washings.

2.2 Preparation of (Bromomethyl)Polystyrene

Scheme 11

5 (Hydroxymethyl)polystyrene (2.50 g, 2.84 mmol, 0.80 mmol/g) and triphenylphosphinedibromide (2.40 g, 5.68 mmol) were combined under nitrogen and 20 ml of dry THF was added. After stirring at room temperature for 24 hr, the resin was filtered and washed extensively with THF (3 x 20 ml), DMF (3 x 20 ml), CH₂Cl₂ (3 x 20 ml), and dried under high vacuum to afford 2.75 g of (bromomethyl)polystyrene as a
 10 beige resin. A loading capacity of 0.58 mmol/g was calculated based on bromide analysis (4.65 % Br).

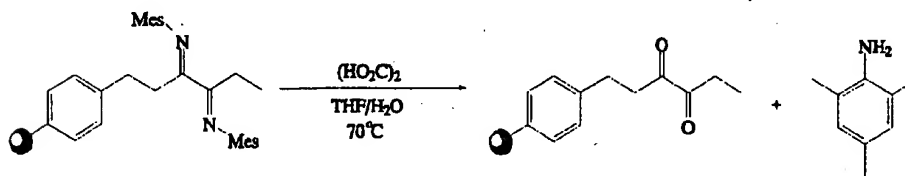
2.3 Alkylation of (2,4,6-Me)₂DAB(Me)Et with (Bromomethyl)Polystyrene

Scheme 12

To a cooled solution (0°C) of (2,4,6-Me)₂DAB(Me)Et (0.50 g, 1.49 mmol) in 15 ml dry THF under nitrogen was added LDA (1.09 ml, 1.49 mmol, 1.5 M in THF). After stirring at 0°C for 2 hr, (bromomethyl)polystyrene (1.06 g, 0.75 mmol) was added and the resulting suspension was stirred for 3 hr at 0°C and 10 hr at room temperature.

The resin was filtered, washed with THF (2 x 10 ml), H₂O (2 x 20 ml), CH₂Cl₂ (2 x 20 ml), and dried under high vacuum to afford 0.60 g of the desired bright yellow resin. The loading capacity of this resin was calculated to be 0.38 mmol/g based on nitrogen analysis (1.07 % N). A strong absorbance at 1635 cm⁻¹ (C=N) is observed by single bead FTIR.

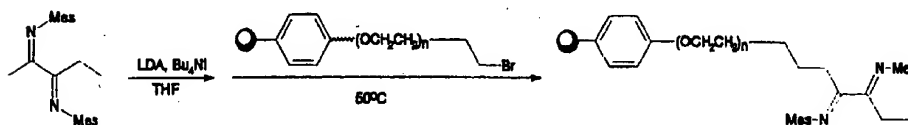
2.4 Hydrolysis of (2,4,6-Me)₃DAB(Me)Et (Methyl)Polystyrene



Scheme 13

- 10 A stirring suspension of (2,4,6-Me)₃DAB(Me)Et (methyl)polystyrene (1.0 g, 0.38 mmol) and oxalic acid (340 mg, 3.80 mmol) in 17 ml THF/H₂O (5:1 v/v) was heated to 70°C for 12 hr. After cooling to room temperature and diluting with 30 ml Et₂O, the resin was filtered and the filtrate was washed with H₂O (2 x 10 ml), dried over MgSO₄, filtered and concentrated to give 24 mg of 2,4,6-trimethylaniline in 98 % yield
- 15 with was >99 % pure by GC/MS analysis and ¹H NMR. The beads were dried under high vacuum to give 850 mg of (2,3-butanedionemethyl)polystyrene. A strong absorbance at 1712 cm⁻¹ (C=O) is observed by single bead FTIR.

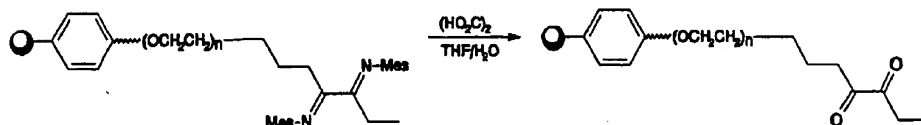
2.5 Alkylation of (2,4,6-Me)₃DAB(Me)Et with (Bromo)PEG Polystyrene



Scheme 14

To a cooled solution (0°C) of (2,4,6-Me)₂DAB(Me)Et (0.70 g, 2.09 mmol) in 15 ml dry THF under nitrogen was added LDA (1.63 ml, 2.44 mmol, 1.5 M in THF). After stirring at 0°C for 4 hr, (bromo) PEG polystyrene (2.33 g, 0.70 mmol, 0.30 mmol/g) and Bu₄NI (0.77 g, 2.09 mmol) were added and the reaction mixture was warmed to 50°C and stirred an additional 8 hr after which the resin was filtered and washed extensively with THF (3 x 20 ml), H₂O (3 x 20 ml), and MeOH (3 x 20 ml). After drying under high vacuum, 2.37 g of (2,4,6-Me)₂DAB(Me)Et (bromo)PEG polystyrene was obtained as a yellow resin. A loading capacity of 0.25 mmol/g was calculated based on nitrogen analysis (0.71 % N). Magic angle spin (MAS) ¹H NMR 400 MHz, (CDCl₃) δ 6.87 (br s, 2H), 3.51 (br s, 2H), 2.76 (br s, 2H), 2.51 (d, 2H, J = 7.6 Hz), 2.28 (s, 6H), 2.01 (s, 12 H), 1.74 (br s, 2 H), 1.03 (t, 3H, J = 6.8 Hz).

2.6 Hydrolysis of (2,4,6-Me)₂DAB(Me)Et PEG Polystyrene



Scheme 15

(2,4,6-Me)₂DAB(Me)Et PEG polystyrene (0.50 g, 0.12 mmol, 0.25 mmol/g) and oxalic acid (0.10 g, 1.12 mmol) was taken up in 20 ml THF/H₂O (5:1 v/v) and heated to 70°C with gentle stirring for 8 hr. After cooling to room temperature and diluting with 25 ml Et₂O, the resin was filtered and the filtrate was washed with H₂O (2 x 10 ml), dried over MgSO₄, filtered and concentrated to give 16 mg of 2,4,6-trimethylaniline in quantitative yield which was >99% pure by GC/MS analysis and ¹H NMR. The beads were dried under high vacuum to afford 450 mg of beige 2,3-butanedione PEG resin. Magic angle spin (MAS) ¹H NMR 400 MHz, (CDCl₃) δ 2.80 (m, 2H), 1.90 (m, 2H), 1.08 (t, 3H, J = 6.8 Hz).



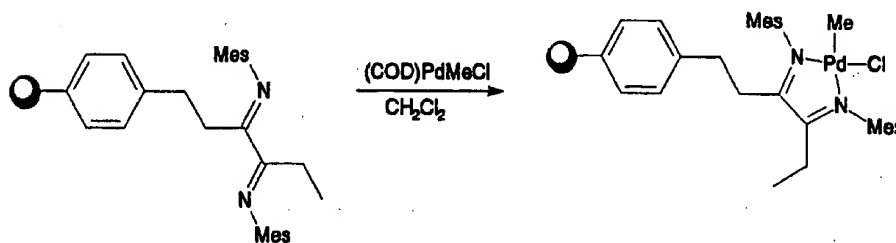
2.8 Preparation of (2,4,6-Me)₂DAB(Me)Et Palladium (II) (Me)Cl PEG Polystyrene



(2,4,6-Me)₂DAB(Me)Et PEG polystyrene (0.50 g, 0.12 mmol, 0.25 mmol/g) and (COD)PdMeCl (0.16 g, 0.63 mmol) were taken up in 7 ml dry CH₂Cl₂,

under nitrogen and stirred at room temperature for 12 hr. The resin was then washed extensively with CH_2Cl_2 to give 0.51 g of $(2,4,6\text{-Me})_2\text{DAB(Me)Et Pd (II) (Me)Cl PEG polystyrene}$ as a reddish-orange resin. Magic angle spin (MAS) $^1\text{H NMR}$ 400 MHz, (CDCl_3) δ 6.97 (br s, 2H), 6.92 (br s, 2H), 2.75 (br s, 2H), 2.45 (br s, 2H), 2.32 (s, 3H), 2.30 (s, 3H), 2.24 (s, 6 H), 2.21 (br s, 6 H), 1.62 (br s, 2H), 1.03 (br s, 3H), 0.36 (s, 3H).

2.9 Preparation of $(2,4,6\text{-Me})_2\text{DAB(Me)Et Palladium (II) (Me)Cl Polystyrene}$



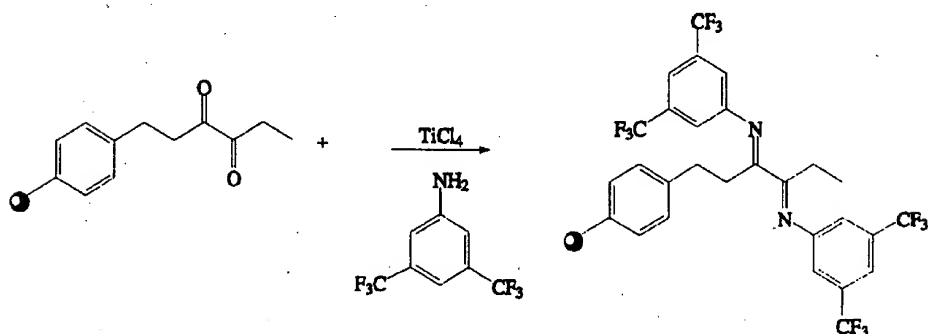
Scheme 18

$(2,4,6\text{-Me})_2\text{DAB(Me)Et polystyrene}$ (0.30 g, 0.11 mmol, 0.38 mmol/g) and $(\text{COD}) \text{PdMeCl}$ (0.15 g, 0.57 mmol) were combined under nitrogen and taken up in 8 ml dry CH_2Cl_2 . After stirring for 10 hr, the resin was washed extensively with CH_2Cl_2 and dried under high vacuum to afford 0.32 g of $(2,4,6\text{-Me})_2\text{DAB(Me)Et palladium (II) (Me)Cl polystyrene}$ as a reddish-orange resin. The loading capacity of this resin was calculated to be 0.32 mmol/g based on palladium analysis (4.15% Pd) and 0.39 mmol/g based on chlorine analysis (3.39% Cl).

Example 2 demonstrates the synthesis of representative diimine ligands utilizing the solid phase combinatorial methods of the present invention. The diimines of Example 2 were synthesized off of the support and subsequently attached to the support prior to undergoing additional modification. Following hydrolysis of the support-attached diimines, a diketone was produced which was utilized for preparation of additional diimine ligands.

EXAMPLE 3

Example 3 illustrates the application of the methods of the present invention to the solid phase synthesis of diimine ligands, wherein the diimine is synthesized on the support.

5 3.1 Solid-Phase Bis-imine Formation

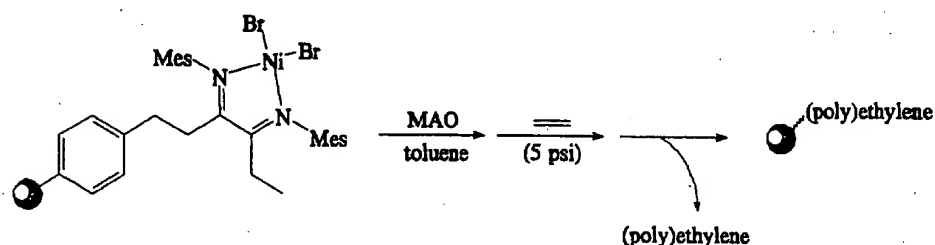
Scheme 19

To a suspension of 2,3 butanedione (methyl)polystyrene (0.10 g, 0.08 mmol) in 5 ml of dry CH₂Cl₂ was added 3,5-bis(trifluoromethyl)aniline (0.25 ml, 1.60 mmol) and TiCl₄ (0.80 ml, 0.80 mmol, 1.0 M in CH₂Cl₂). The mixture was stirred at room temperature for 24 hr upon which the resin was filtered and washed extensively with CH₂Cl₂ (3 x 10 ml), MeOH (3 x 10 ml), H₂O (3 x 10 ml), and dried under high vacuum to give 0.11 g of the desired resin. The loading capacity of this resin was calculated to be 0.15 mmol/g based on nitrogen analysis (0.43 % N).

Example 3 demonstrated that diimines can be formed directly on a resin which has been functionalized with a diketone.

EXAMPLE 4

Example 4 illustrates the utility of the catalysts of the present invention in polymerizing olefins. Both the supported and unsupported catalysts of the invention were assayed for their ability to polymerize ethylene to poly(ethylene). The polymerization of higher olefins such as hexene was also examined.

4.1 Polymerization of Ethylene

Scheme 20

The above resin-bound nickel(II) dibromide complex (0.16 g, 0.03 mmol) was suspended in 10 ml dry toluene upon which MAO was added (2.00 ml, 300.0 mmol, 10 % wt in toluene). The resin immediately turned dark blue. After stirring for 1 hr, ethylene gas was bubbled through the suspension for 1 min and then the reaction vessel was sealed to a pressure of 5 psi. An internal thermocouple measured a 29°C exotherm over a 20 min period. After stirring for an additional 1.5 hr, the temperature slowly dropped back to room temperature and the viscous solution was filtered and the beads were washed with toluene (3 x 10 ml). The filtrate was concentrated and then quenched with MeOH upon which white rubber-like (poly)ethylene formed immediately. This material was filtered and dried to give 1.60 g of (poly)ethylene. The beads were dried under high vacuum and afforded 1.60 g of material corresponding to a 10-fold mass increase of the polystyrene beads.

An identical procedure was performed with the exception that the MAO activated catalyst was washed with toluene (3 x 10 ml). After the excess MAO was filtered off, the resin-bound catalyst was taken up in 10 ml toluene prior to the

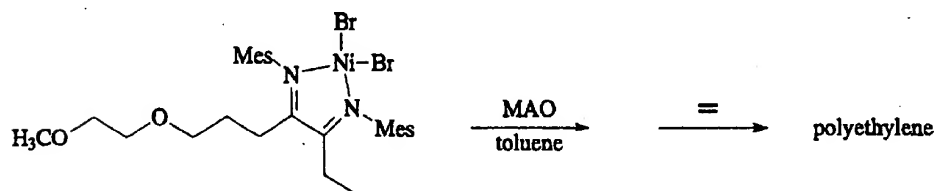
introduction of ethylene. An identical outcome was obtained to that described earlier. When this washed resin was taken up in 10 ml dry hexane instead of toluene, less (poly)ethylene was obtained on the bead as well in the filtrate, both weighing 0.26 g.

The above example demonstrated that the supported catalysts of the present invention can catalyze the polymerization of olefins.

4.2 Ethylene polymerization with [2-Ph]PMI(2,6-(Pr)₂Ph)]NiBr₂/MAO

To a suspension of 6 mg (0.01 mmol) of [2-Ph]PMI(2,6-(Pr)₂Ph)]NiBr₂ in 5 mL of anhydrous, degassed toluene was added 3.3 mL (5 mmol) of 10% MAO in toluene and the resultant green solution was stirred at RT for 1h. This solution was then flushed with ethylene and stirred under 10 psi of ethylene for 2 h. To the reaction mixture was added 4 M HCl (50 mL) and Et₂O (100 mL), the layers were separated, and the organic layer was dried over MgSO₄. Removal of the volatiles by rotary evaporation provided 1.3 g of polymeric material.

4.3 Polymerization of Ethylene with (2,4,6-Me)₂DAB(1-Methoxyethoxypropyl)Et Nickel (II) Dibromide

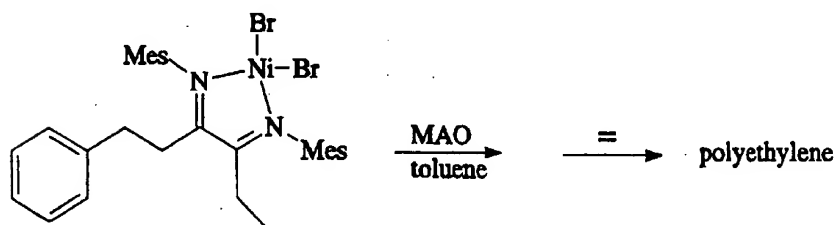


Scheme 21

(2,4,6-Me)₂DAB(1-methoxyethoxypropyl)ethyl nickel (II) dibromide (0.02 g, 0.03 mmol) was suspended in 15 ml dry toluene upon which MAO was added (2.00 ml, 300.0 mmol, 10% wt in toluene). The solution turned dark blue over a 1 hour period. After stirring for 1 hr, ethylene gas was bubbled through the suspension for 1 min and then the reaction vessel was sealed to a pressure of 5 psi. An internal thermocouple measured a 23°C exotherm over a 45 min period. After stirring for an

additional 1.5 hr, the temperature slowly dropped back to room temperature and the solution was quenched with MeOH followed by 5 N HCl. The precipitated polyethylene was collected by filtration and afforded 1.38 g of polyethylene after drying under high vacuum.

5 4.4 Polymerization of Ethylene with (2,4,6-Me)₂DAB(Me)EtPh Nickel (II) Dibromide

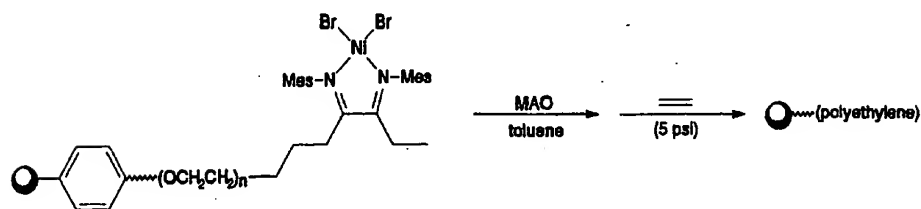


Scheme 22

(2,4,6-Me)₂DAB(Me)EtPh nickel (II) dibromide (0.02 g, 0.03 mmol) was suspended in 15 ml dry toluene upon which MAO was added (2.00 ml, 9.33 mmol, 10% wt in toluene). The solution turned dark blue over a 1 hour period. After stirring for 1 hr, ethylene gas was bubbled through the suspension for 1 min and then the reaction vessel was sealed to a pressure of 5 psi. An internal thermocouple measured a 19°C exotherm over a 45 min period. After stirring for an additional 1.5 hr, the temperature slowly dropped back to room temperature and the solution was quenched with MeOH followed by 5 N HCl. The precipitated polyethylene was collected by filtration and afforded 2.10 g of polyethylene after drying under high vacuum.

The above examples demonstrated the utility of the supported and unsupported catalysts of the present invention in olefin polymerization reactions.

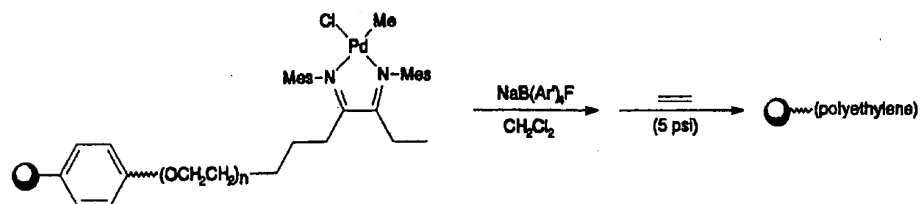
4.5 Polymerization of Ethylene with (2,4,6-Me)₃DAB(Me)Et Nickel (II) Dibromide PEG Polystyrene



Scheme 23

- 5 The above resin-bound nickel(II) dibromide resin (0.20 g, 0.02 mmol, 0.10 mmol/g) was suspended in 20 ml dry toluene upon which MAO was added (2.00 ml, 300.0 mmol, 10% wt in toluene). The resin immediately turned dark blue. After stirring for 1 hr, ethylene gas was bubbled through the suspension for 1 min and then the reaction vessel was sealed to a pressure of 5 psi. An internal thermocouple measured a 3°C
- 10 exotherm over a 45 min period. After stirring for an additional 1.5 hr, the temperature slowly dropped back to room temperature and the solution was filtered and the beads were washed with toluene (3 x 10 ml). The beads were dried under high vacuum and afforded 0.67 g of material corresponding to a 3-fold mass increase of the polystyrene beads. The filtrate afforded no polyethylene.

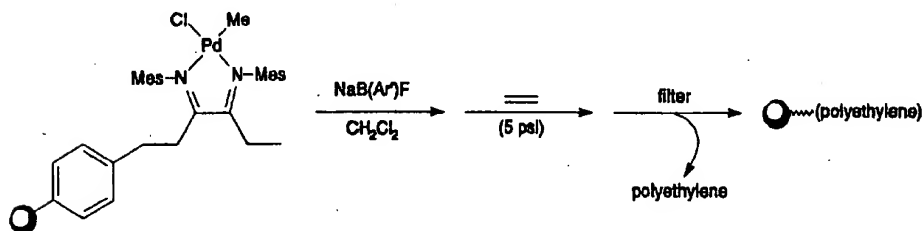
15 4.6 Polymerization of Ethylene with (2,4,6-Me)₃DAB(Me)Et Palladium (II) (Me)Cl PEG Polystyrene



Scheme 24

The above resin-bound palladium (II) (Me)Cl resin (0.20 g, 0.02 mmol, 0.10 mmol/g) was suspended in 20 ml dry CH_2Cl_2 upon which $\text{NaB}(\text{Ar}')_4\text{F}$ was added (18 mg, 0.02 mmol). The resin turned brownish-red over a 1 hr period upon which ethylene gas was bubbled through the suspension for 1 min. The reaction vessel was sealed to a pressure of 5 psi. No exotherm was observed throughout the course of the reaction. After stirring for an additional 1.5 hr, the solution was filtered and the beads were washed with toluene (3 x 10 ml). The beads were dried under high vacuum and afforded 0.25 g of material corresponding to a 20% mass increase of the polystyrene beads. The filtrate afforded no polyethylene.

4.7 Polymerization of Ethylene with (2,4,6-Me)₂DAB(Me)Et Palladium (II) (Me)Cl Polystyrene

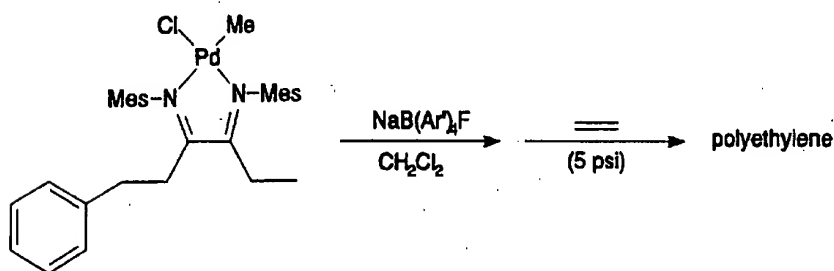


Scheme 25

The above resin-bound palladium (II) (Me)Cl resin (0.10 g, 0.03 mmol, 0.32 mmol/g) was suspended in 25 ml dry CH_2Cl_2 upon which $\text{NaB}(\text{Ar}')_4\text{F}$ was added (30 mg, 0.03 mmol). The resin turned brownish-red over a 1 hr period upon which ethylene gas was bubbled through the suspension for 1 min. The reaction vessel was sealed to a pressure of 5 psi. A 23°C was observed throughout the course of the reaction. After stirring for an additional 1.5 hr, the solution was filtered and the beads were washed with toluene (3 x 10 ml). The beads were dried under high vacuum and afforded 0.25 g of material corresponding to a 100% mass increase of the polystyrene beads. Workup of the filtrate afforded 2.28 g of polyethylene as a colorless gum. Gel permeation

chromatography (toluene, 23°C, polystyrene reference): $M_n = 18,518$; $M_w = 31,811$; $M_w/M_n = 1.72$.

4.8 Polymerization of Ethylene with (2,4,6-Me)₂DAB(Me)Et Palladium (II) (Me)Cl



Scheme 26

(2,4,6-Me)₂DAB(Me)Et Palladium (II) (Me)Cl (0.02 g, 0.03 mmol) was dissolved in 25 ml dry CH_2Cl_2 upon which $\text{NaB(Ar')}_4\text{F}$ was added (30 mg, 0.03 mmol). The solution turned brownish-red over a 1 hr period upon which ethylene gas was bubbled through the suspension for 1 min. The reaction vessel was sealed to a pressure of 5 psi. A 28°C exotherm was observed throughout the course of the reaction. After stirring for an additional 2.5 hr, the solution was filtered through celite. Workup of the filtrate afforded 3.50 g of polyethylene as a colorless gum. Gel permeation chromatography (toluene, 23°C, polystyrene reference): $M_n = 21,016$; $M_w = 31,471$; $M_w/M_n = 1.50$.

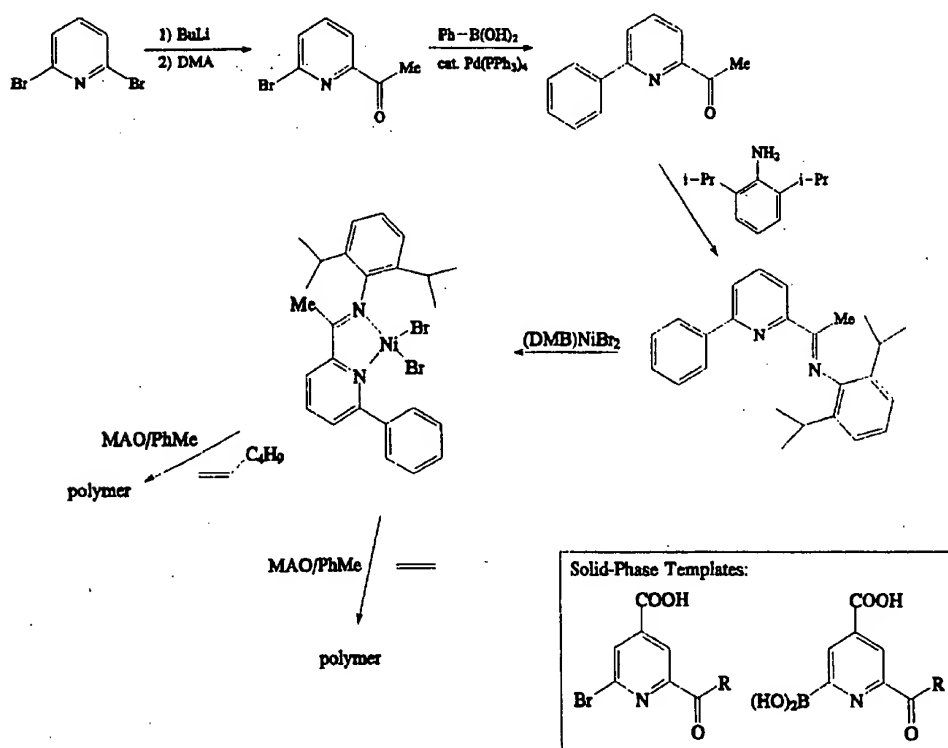
4.9 Hexene polymerization with [2-Ph]PMI(2,6-(Pr)₂Ph)]NiBr₂/MAO

To a suspension of 6 mg (0.01 mmol) of [2-Ph]PMI(2,6-(Pr)₂Ph)]NiBr₂ in 1 mL of anhydrous, degassed toluene was added 3.3 mL (5 mmol) of 10% MAO in toluene and the resultant green solution was stirred at RT for 1h. To this solution was then added 8.4 g (100 mmol) of hexene and the solution was stirred under N_2 for 24 h. To the reaction mixture was added 4 M HCl (50 mL) and Et_2O (100 mL), the layers were

separated, and the organic layer was dried over MgSO_4 . Removal of the volatiles by rotary evaporation provided 3.9 g (46%) of polymeric material.

EXAMPLE 5

Example 5 details the preparation of a pyridyl imine ligand and its nickel complex. The catalyst was used to polymerize both hexene and ethylene. The synthetic route to the pyridyl imine nickel complex is displayed in Scheme 27.



Scheme 27

10 5.1 Preparation of 2-acetyl-6-bromopyridine

To a solution of 3.00 g (12.7 mmol) of 2,6-dibromopyridine in 20 mL anhydrous Et_2O at -78°C was added dropwise over 30 min. 8.0 mL (12.8 mmol) of 1.6 M *n*-BuLi in cyclohexane. After stirring for 3 h at -78°C , 8.2 mL (88 mmol) of *N,N*-dimethylacetamide was added dropwise and the solution was stirred at -78°C for 1 h. On

warming to RT, Et₂O (100 mL) and saturated aqueous NH₄Cl (50 mL) were added and the layers were separated. The organic layer was dried over Na₂SO₄ and the volatiles were removed by rotary evaporation. The resulting yellow solid was recrystallized from hexanes to provide 1.8 g (71%) of 2-acetyl-6-bromopyridine as colorless crystals. ¹H NMR (CDCl₃): δ 2.81 (s, 3H); 7.67-7.77 (m, 2 H); 8.22 (dd, *J* = 6.8, 1.6 Hz, 1 H).
5 Mass Spec.: *m/e* 200.

5.2 Preparation of 2-acetyl-6-phenylpyridine

To a Schlenk tube charged with a solution of 200 mg (1.0 mmol) of 2-acetyl-6-bromopyridine and 23 mg (0.02 mmol) of (Ph₃P)₄Pd in 10 mL of degassed
10 toluene was added a solution of 150 mg (1.2 mmol) phenylboronic acid and 270 mg (2.5 mmol) Na₂CO₃ in 8 mL of degassed 4:1 H₂O/MeOH. The biphasic mixture was heated to 80°C with rapid stirring for 1 h. On cooling to RT, Et₂O (50 mL) was added and the layers were separated. The organic layer was dried over Na₂SO₄ and the volatiles were removed by rotary evaporation. The resulting oil was chromatographed on silica with 10-
15 50% CH₂Cl₂/hexanes eluent to provide 176 mg (89%) of 2-acetyl-6-phenylpyridine as a white powder. ¹H NMR (CDCl₃): δ 2.84 (s, 3H); 7.43-7.62 (m, 3 H); 7.91-8.08 (m, 3 H); 8.18 (d, *J* = 6.6 Hz, 2H). Mass Spec.: *m/e* 197.

5.3 Preparation of 2-acetyl-6-phenylpyridine 2,6-di(Isopropyl)phenyl imine [(2-Ph)PMI(2,6-(Pr)₂Ph)]

20 A solution of 197 mg (mmol) of 2-acetyl-6-phenylpyridine and 266 mg (1.5 mmol) of 2,6-diisopropylaniline in 5 mL anhydrous MeOH and 0.1 mL of 0.1 M H₂SO₄ in MeOH was heated to 50°C for 12h. The volatiles were removed by rotary evaporation and the crude material chromatographed on silica with 5% EtOAc/hexanes eluent to provide 287 mg (80%) of (2-Ph)PMI(2,6-(Pr)₂Ph) as a yellow solid. ¹H NMR (CDCl₃):
25 δ 1.17 (ddd, *J* = 4.6, 1.7, 0.7 Hz, 12H); 2.23 (d, *J* = 2.5 Hz, 3 H); 2.73 (dq, *J* = 6.8, 2.5 Hz); 7.10-7.25 (m, 3 H); 7.60-7.75 (m, 2 H); 7.90-8.06 (m, 2 H); 8.33-8.40 (m, 1 H). Mass Spec.: *m/e* 356.

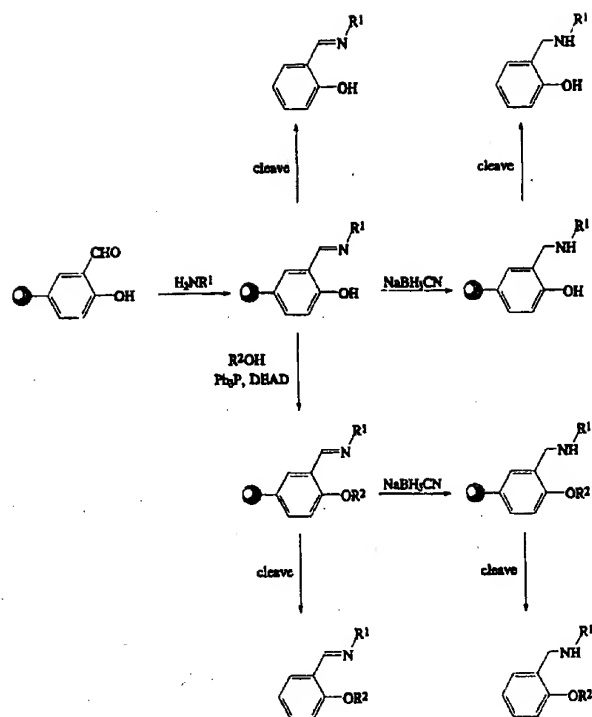
5.4 Preparation of [(2-Ph)PMI(2,6-(Pr)₂Ph)]NiBr₂

A suspension of 71 mg (0.2 mmol) (2-Ph)PMI(2,6-(Pr)₂Ph) and 62 mg (0.2 mmol) of (dimethoxyethane)nickel(II)bromide in anhydrous CH₂Cl₂ was stirred at RT under N₂ for 48 h. The volatiles were removed by rotary evaporation and the solid was washed several times with hexanes to provide 101 mg (88 %) of 1 [(2-Ph)PMI(2,6-(Pr)₂Ph)]NiBr₂ as an orange powder.

The above example demonstrated that pyridyl imines can be prepared by the methods of the present invention and that these imines are of use in polymerizing olefins. Solid phase analogues of the above catalysts are prepared using the starting materials shown in Scheme 13 (inset), above.

EXAMPLE 6

This example illustrates reaction schemes which can be used to prepare a variety of [2,0], [2,1], and [2,2] ligand libraries. Such [2,0], [2,1], and [2,2] ligand libraries can be prepared using solution or solid phase methodologies from a salen-based scaffold using the synthetic method outlined in Scheme 14, wherein R¹ and R² are defined as in the section above describing diimine libraries.



Scheme 28

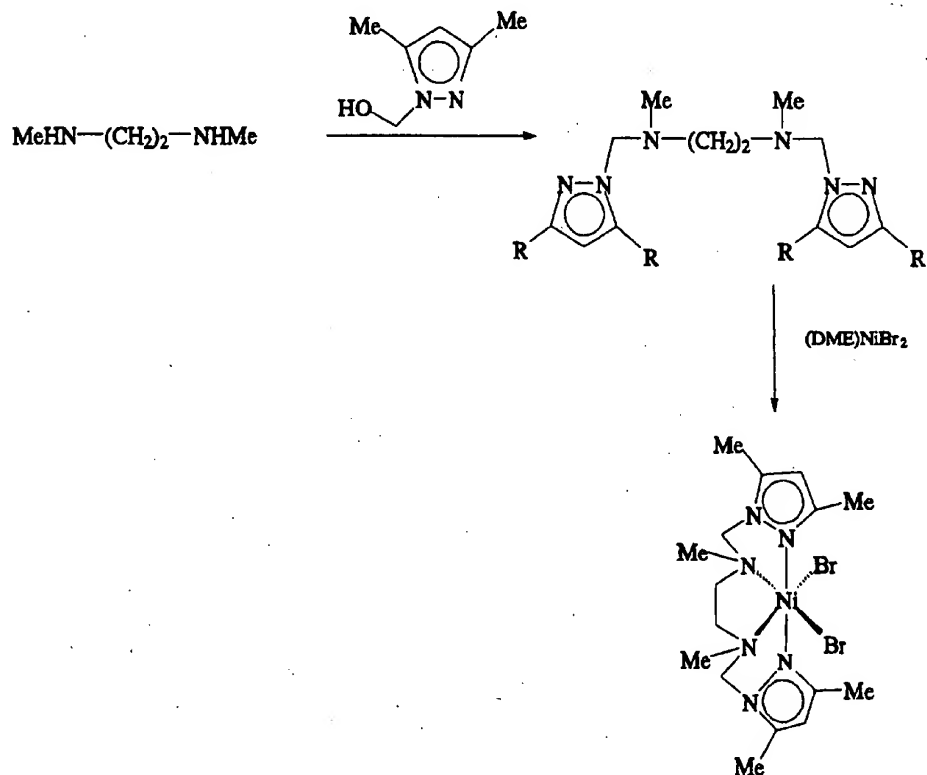
Scheme 28 describes chemistry relevant to both solution and solid phase methodologies. When this chemistry is performed via solid phase chemistries the scaffold is bound to a solid particle represented by the ball in the above figure.

The [2,0] ligand libraries can be converted into organometallic libraries using the displacement or oxidative addition methods described above for the diimine systems. The [2,1] ligand libraries can be converted into organometallic libraries using oxidative addition or metathesis reactions. Oxidative addition of the heteroatom - proton bound to a low valent metal precursor to form a hydride or hydrocarbyl ligand-metal complex is an effective method of creating reactive organometallic libraries. Metathesis reactions are also useful for producing organometallic libraries from [2,1] ligand libraries. The Bronsted acidic libraries described in the above figure can be used directly in metathesis reactions by contacting said libraries with metal reagents (including main group alkyls such as trimethylaluminum) containing leaving group ligands capable of abstracting

the acidic proton on the [2,1] ligand. Alternatively, the [2,1] ligand libraries can be deprotonated to form metal salt libraries, which can be further reacted with metal complexes to undergo a metathesis reaction. Other metathesis reactions, such as those resulting in the loss of tin or silyl byproduct can also be envisioned.

5 Diamide based organometallic libraries can be prepared from diamino ligand libraries using oxidative addition or metathesis reactions similar to those described above. The diamino ligand libraries can be prepared using the synthetic procedure described in Figures 2B, 7, and 11.

10 Tetradentate [4,0] ligand libraries can be constructed by combining two [2,0] ligand fragments as illustrated in Scheme 15. One example of such a combination, is illustrated in the figure below. [4,0] ligand-metal libraries can be prepared by contacting the [4,0] ligand with a suitable transition metal precursor in a manner similar to that described for the preparation of [2,0] bis-imine-metal libraries.



It is to be understood that the above description is intended to be illustrative and not restrictive. Many embodiments will be apparent to those of skill in the art upon reading the above description. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be

5 determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled. The disclosures of all articles and references, including patent applications and publications, are incorporated herein by reference for all purpose.

WHAT IS CLAIMED IS:

1 1. A method of making an array of metal-ligand compounds, said
2 method comprising:

3 (a) synthesizing a first metal-binding ligand and a second metal-binding
4 ligand on first and second regions on a substrate; and

5 (b) delivering a first metal ion to said first metal-binding ligand and a
6 second metal ion to said second metal-binding ligand to form a first
7 metal-ligand compound and a second metal-ligand compound.

1 2. The method as recited in claim 1 further comprising the step of
2 (c) activating said first metal-ligand compound with a first activator to
3 form a first activated metal-ligand compound and said second metal-
4 ligand compound with a second activator to form a second activated
5 metal-ligand compound.

1 3. The method as recited in claim 1 wherein step (a) comprises:
2 (i) synthesizing a first component of said first metal-binding ligand and a
3 first component of said second metal-binding ligand on first and
4 second regions of said substrate; and
5 (ii) synthesizing a second component of said first metal-binding ligand and
6 a second component of said second metal-binding ligand on said
7 first and second regions of said substrate.

1 4. The method as recited in claim 2 wherein said first and second
2 activated metal-ligand compounds are organometallic compounds.

1 5. The method as recited in claim 2 wherein said first and second
2 activated metal-ligand compounds are homogeneous catalysts.

1 6. The method as recited in claim 5 wherein said homogeneous
2 catalysts are polymerization catalysts.

1 7. The method as recited in claim 2 wherein said first and second
2 activated metal-ligand compounds are heterogeneous catalysts.

1 8. The method as recited in claim 1 wherein said first and second
2 metal-ligand compounds are metallocene compounds.

1 9. The method as recited in claim 1 wherein said first and second
2 metal-ligand compounds are activator-free catalysts.

1 10. The method as recited in claim 9 wherein said activator-free
2 catalysts are homogeneous catalysts.

1 11. The method as recited in claim 9 wherein said activator-free
2 catalysts are heterogeneous catalysts.

1 12. The method as recited in claim 1 wherein said first said second
2 metal-binding ligands are neutral bidentate ligands.

1 13. The method as recited in claim 1 wherein said first and second
2 metal-binding ligands are monoanionic bidentate ligands.

1 14. The method as recited in claim 1 wherein said first and second
2 metal-binding ligands are chelating diamine ligands.

1 15. The method as recited in claim 14 wherein said chelating diamine
2 ligands are 1,2-diamine ligands.

1 16. The method as recited in claim 1 wherein said first and second
2 metal-binding ligands are salen ligands.

1 17. The method as recited in claim 1 wherein said first and second
2 metal-binding ligands are ancillary ligands.

1 18. The method as recited in claim 1 wherein said first and second
2 metal-binding ligands have a coordination number (CN) independently selected from the
3 group consisting of 1, 2 and 3.

1 19. The method as recited in claim 1 wherein said first and second
2 metal-binding ligands have a charge independently selected from the group consisting of
3 0, -1, -2, -3 and -4.

1 20. The method as recited in claim 1 wherein said first and second
2 metal-binding ligands have a coordination number (CN) and charge independently selected
3 from the group consisting of (i) CN = 2, charge = -2; (ii) CN = 2, charge = -1; (iii)
4 CN = 1, charge = -1; (iv) CN = 2, charge = neutral; (v) CN = 3, charge = -1; (vi)
5 CN = 1, charge = -2; (vii) CN = 3, charge = -2; (viii) CN = 2, charge = -3; and (ix)
6 CN = 3, charge = -3.

1 21. The method as recited in claim 1 wherein said first and second
2 metal-binding ligands are ancillary ligands each having a charge that is greater than the
3 coordination number.

1 22. The method as recited in claim 1 wherein said first and second
2 metal ions are each transition metal ions.

1 23. The method as recited in claim 22 wherein said first and second
2 metal-binding ligands are neutral bidentate ligands, and each of said transition metal ions
3 is stabilized by a labile neutral Lewis base.

1 24. The method as recited in claim 22 wherein said first and second
2 metal-binding ligands are chelating diamine ligands, and each of said transition metal ions
3 is a Group 10 transition metal.

1 25. The method as recited in claim 22 wherein said first and second
2 metal-binding ligands are monoanionic bidentate ligands, and each of said transition metal
3 ions is stabilized by a labile anionic leaving group ligand.

1 26. The method as recited in claim 2 wherein said first and second
2 activators are independently selected from the group consisting of MAO, $[Q]^+[NCA]^-$,
3 $[H(OEt_2)]^+[BAR_4]^-$ and $[H(OEt_2)]^+[B(C_6F_5)_4]^-$.

1 27. The method as recited in claim 2 wherein said first and second
2 activators are independently selected and become counterions after activation.

1 28. The method as recited in claim 1 wherein said first and second
2 metal ions are independently selected from the group consisting of Pd, Ni, Pt, Ir, Rh, Cr,
3 Mo, W and Co.

1 29. The method as recited in claim 1 wherein said first and second
2 metal-binding ligands are supported.

1 30. The method as recited in claim 29 wherein said first and second
2 metal-binding ligands are attached directly to said substrate.

1 31. The method as recited in claim 29 wherein said first and second
2 metal-binding ligands are attached to said substrate through first and second linker
3 groups.

1 32. The method as recited in claim 29 wherein said first and second
2 metal-binding ligands are attached to first and second synthesis support on said substrate.

1 33. The method as recited in claim 32 wherein said first and second
2 metal-binding ligands are attached directly to said first and second synthesis support.

1 34. The method as recited in claim 32 wherein said first and second
2 metal-binding ligands are attached to said first and second synthesis support through first
3 and second linker groups.

1 35. The method as recited in claim 1 wherein said first and second
2 metal-binding ligands are unsupported.

1 36. The method as recited in claim 1 further comprising the step of
2 screening said array of metal-ligand compounds for a useful property.

1 37. The method as recited in claim 36 wherein said useful property is
2 a polymerization characteristic.

1 38. The method as recited in claim 36 wherein said useful property is
2 a mechanical property.

1 39. The method as recited in claim 36 wherein said useful property is
2 an optical property.

1 40. The method as recited in claim 36 wherein said useful property is
2 a physical property.

1 41. The method as recited in claim 36 wherein said useful property is
2 a morphological property.

1 42. The method as recited in claim 36 wherein said useful property is
2 the lifetime of said metal-ligand compounds.

1 43. The method as recited in claim 36 wherein said useful property is
2 the stability of said metal-ligand compounds with respect to specific reaction conditions.

1 44. The method as recited in claim 36 wherein said useful property is
2 the selectivity of said metal-ligand compounds for a particular reaction.

1 45. The method as recited in claim 36 wherein said useful property is
2 the conversion efficiency of said metal-ligand compounds for a particular reaction.

1 46. The method as recited in claim 36 wherein said useful property is
2 the activity of said metal-ligand compounds for a particular reaction.

1 47. The method as recited in claim 1 wherein said substrate has a
2 configuration selected from the group consisting of: (i) a porous or non-porous substrate,
3 wherein a sample chamber is filled with reactant gas at pressure P and each of said
4 catalysts is selectively activated; and (ii) a porous substrate, wherein reactant gas at
5 pressure P is driven through the supported catalyst and substrate into a region of lower
6 pressure, wherein each of said catalysts is selectively activated.

1 48. The method as recited in claim 1 wherein the components of said
2 homogeneous catalysts are delivered to a synthesis support material contained on said
3 substrate, said synthesis support material and said substrate having a configuration
4 selected from the group consisting of (i) a porous or non-porous synthesis support
5 material contained in wells wherein the components flow to or from the top of said wells
6 through a hole in the bottom of said wells; (ii) a porous or non-porous synthesis support
7 material contained in wells wherein the components flow into and out of the top of said
8 wells; and (iii) a porous or non-porous support which serves as both said synthesis
9 support material and said substrate, wherein the components are deposited directly onto
10 the surface of said substrate.

1 49. The method as recited in claim 36 wherein said array is screened
2 in a manner selected from the group consisting of: (i) screening said array
3 simultaneously, (ii) screening said array serially; and (iii) screening said array in a
4 spatially selective manner, wherein the detector is distanced from said array, said array is
5 screened, and then the detector is repositioned so that a portion of said array is screened.

1 50. The method as recited in claim 36 wherein said useful property is
2 screened for using a technique selected from the group consisting of scanned mass
3 spectrometry, chromatography, ultraviolet imaging, visible imaging, infrared imaging,
4 electromagnetic imaging, ultraviolet spectroscopy, visible spectroscopy, infrared
5 spectroscopy, electromagnetic spectroscopy and acoustical methods.

1 51. The method as recited in claim 1 wherein each of said metal-
2 ligand compounds is synthesized in an area of less than 25 cm².

1 52. The method as recited in claim 1 wherein each of said metal-
2 ligand compounds is synthesized in an area of less than 10 cm².

1 53. The method as recited in claim 1 wherein each of said metal-
2 ligand compounds is synthesized in an area of less than 1 cm².

1 54. The method as recited in claim 1 wherein each of said metal-
2 ligand compounds is synthesized in an area of less than 1 mm².

1 55. The method as recited in claim 1 wherein each of said metal-
2 ligand compounds is synthesized in an area of less than 10,000 μm².

1 56. The method as recited in claim 1 wherein each of said metal-
2 ligand compounds is synthesized in an area of less than 1,000 μm².

1 57. The method as recited in claim 1 wherein each of said metal-
2 ligand compounds is synthesized in an area of less than 100 μm^2 .

1 58. The method as recited in claim 1 wherein each of said metal-
2 ligand compounds is synthesized in an area of less than 1 μm^2 .

1 59. The method as recited in claim 1 wherein at least 10 different
2 metal-ligand compounds are synthesized on said substrate.

1 60. The method as recited in claim 1 wherein at least 20 different
2 metal-ligand compounds are synthesized on said substrate.

1 61. The method as recited in claim 1 wherein at least 50 different
2 metal-ligand compounds are synthesized on said substrate.

1 62. The method as recited in claim 1 wherein at least 100 different
2 metal-ligand compounds are synthesized on said substrate.

1 63. The method as recited in claim 1 wherein at least 200 different
2 metal-ligand compounds are synthesized on said substrate.

1 64. The method as recited in claim 1 wherein at least 500 different
2 metal-ligand compounds are synthesized on said substrate.

1 65. The method as recited in claim 1 wherein at least 1,000 different
2 metal-ligand compounds are synthesized on said substrate.

1 66. The method as recited in claim 1 wherein at least 10,000 different
2 metal-ligand compounds are synthesized on said substrate.

1 67. The method as recited in claim 1 wherein at least 10^6 different
2 metal-ligand compounds are synthesized on said substrate.

1 68. The method as recited in claim 1 wherein said first and second
2 metal-binding ligands are [2,2] or [2,1] ligands and wherein each of said metal-binding
3 ligands is contacted with a main group metal alkyl complex such that said first and second
4 metal-ligand compounds are each in the mono- or di-protic form.

1 69. The method as recited in claim 68 wherein said main group metal
2 alkyl complex is a trialkylaluminum complex.

1 70. A method as recited in claim 68 wherein said array of metal-ligand
2 compounds is useful for an organic transformation reaction requiring Lewis acidic sites.

1 71. A method as recited in claim 70 wherein said organic
2 transformation reaction is selected from the group consisting of stereo-selective coupling
3 reactions, olefin oligomerization reactions and olefin polymerization reactions.

1 72. The method as recited in claim 68 wherein said array of metal-
2 ligand compounds is further modified by reaction with an ion-exchange activator to
3 produce an array of ligand-stabilized cationic aluminum reagents.

1 73. The method as recited in claim 72 wherein said ion-exchange
2 activator is $[\text{PhNMe}_2\text{H}][\text{B}(\text{C}_6\text{F}_5)_4]$.

1 74. The method as recited in claim 72 wherein said ligand-stabilized
2 cationic aluminum reagents can be used as catalysts for a reaction selected from the group
3 consisting of organic coupling reactions, olefin oligomerization reactions and olefin
4 polymerization reactions.

1 75. The method as recited in claim 1 wherein the components of said
2 first and second metal-ligand compounds are delivered to said substrate using a liquid
3 dispensing techniques in combination with a masking technique.

1 76. A method for preparing a polymer blend, said method comprising
2 contacting at least two metal-ligand compounds prepared in accordance with the method
3 recited in claim 1 with a cocatalyst and a monomer.

1 77. A method for polymerizing olefins, diolefins and acetylenically
2 unsaturated monomers, said method comprising contacting at least one metal-ligand
3 compounds prepared in accordance with the method recited in claim 1 with a cocatalyst
4 and a monomer.

1 78. A method of making an array of metal-ligand compounds, said
2 method comprising:
3 (a) delivering a first metal-binding ligand and a second metal-binding ligand
4 on first and second regions on a substrate; and
5 (b) delivering a first metal ion to said first metal-binding ligand and a
6 second metal ion to said second metal-binding ligand to form a first
7 metal-ligand compound and a second metal-ligand compound.

1 79. A method of making and screening an array of metal-ligand
2 compounds, said method comprising:
3 (a) synthesizing a spatially segregated array of ligands;
4 (b) delivering a suitable metal precursor to each element of said array of
5 ligands to create an array of metal-ligand compounds;
6 (c) optionally activating said array of metal-ligand compounds with a
7 suitable cocatalyst;
8 (d) optionally modifying said array of metal-ligand compounds with a third
9 component; and

10 (e) screening said array of metal-ligand compounds for a useful property
11 using a parallel or rapid serial screening technique selected from the group consisting of
12 optical imaging, optical spectroscopy, mass spectrometry, chromatography, acoustic
13 imaging, acoustic spectroscopy, infrared imaging and infrared spectroscopy.

1 80. An array of at least 10 different metal-ligand compounds at known
2 locations on a substrate.

1 81. The array as recited in claim 80 wherein said array contains more
2 than 20 different metal-ligand compounds at known locations on said substrate.

1 82. The array as recited in claim 80 wherein said array contains more
2 than 50 different metal-ligand compounds at known locations on said substrate.

1 83. The array as recited in claim 80 wherein said array contains more
2 than 100 different metal-ligand compounds at known locations on said substrate.

1 84. The array as recited in claim 80 wherein said array contains more
2 than 200 different metal-ligand compounds at known locations on said substrate.

1 85. The array as recited in claim 80 wherein said array contains more
2 than 500 different metal-ligand compounds at known locations on said substrate.

1 86. The array as recited in claim 80 wherein said array contains more
2 than 1,000 different metal-ligand compounds at known locations on said substrate.

1 87. The array as recited in claim 80 wherein said array contains more
2 than 10,000 different metal-ligand compounds at known locations on said substrate.

1 88. The array as recited in claim 80 wherein said array contains more
2 than 10^6 different metal-ligand compounds at known locations on said substrate.

- 1 89. The array as recited in claim 80 wherein each of the metal-ligand
- 2 compounds of said array has similar functionality, thereby allowing the metal-ligand
- 3 compounds of said array to be compared for a selected property.

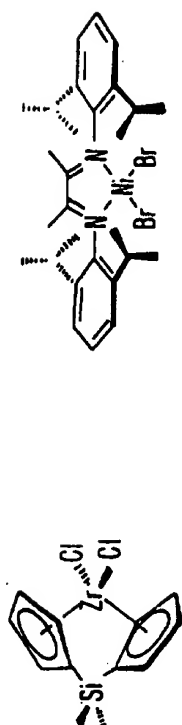


FIG. 1.

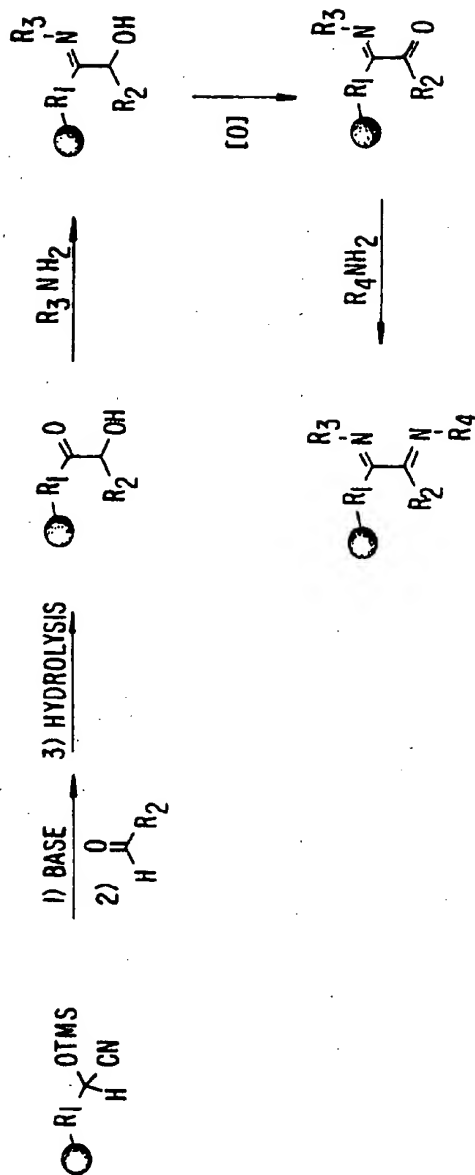


FIG. 2A.

2/19

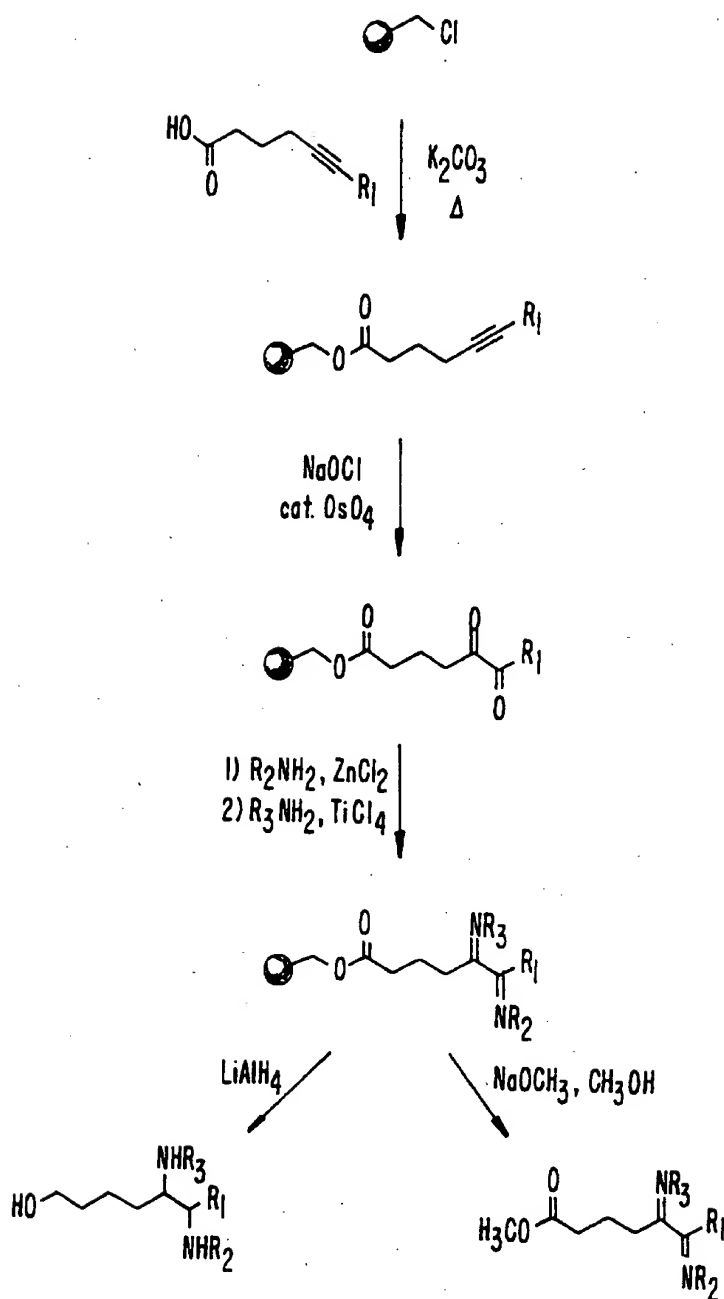


FIG. 2B.

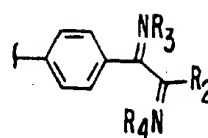
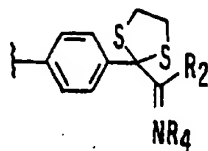
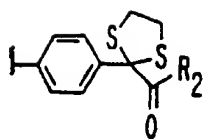
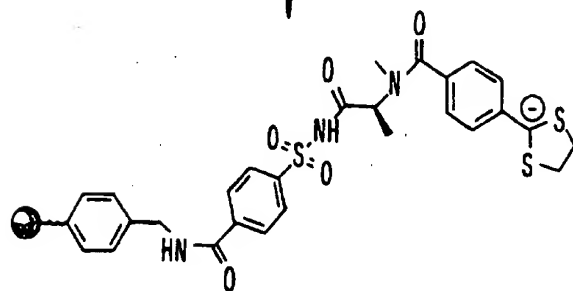
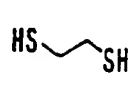
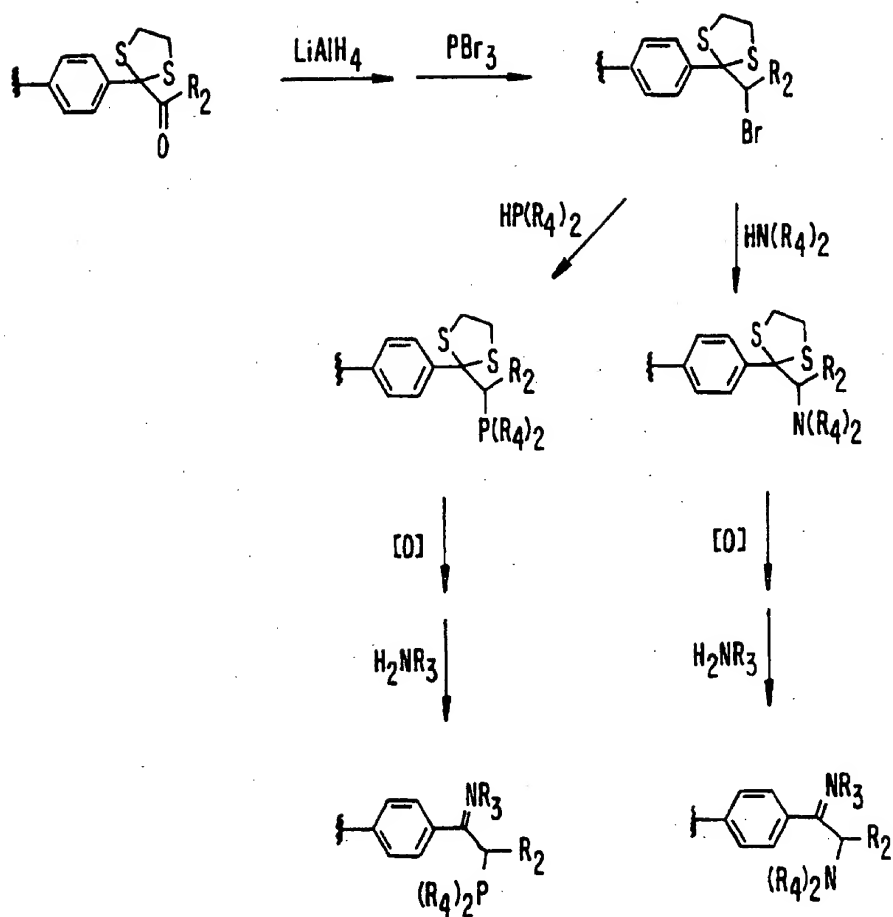
C[C@H](NC(=O)c1ccc(C=O)cc1)S(=O)(=O)C(=O)Nc1ccc(cc1)C2=CC=CC=C2

FIG 3A.

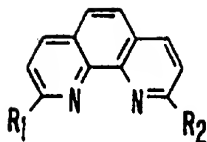
4/19

**FIG. 3B.**

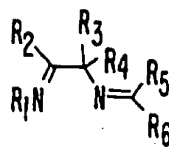
5/19



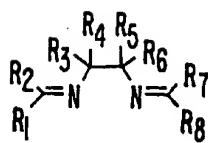
A



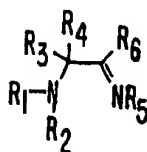
B



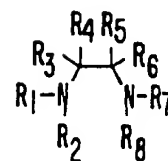
C



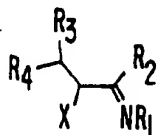
D



E



F



G

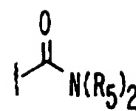
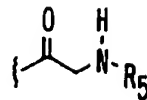
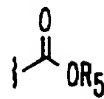
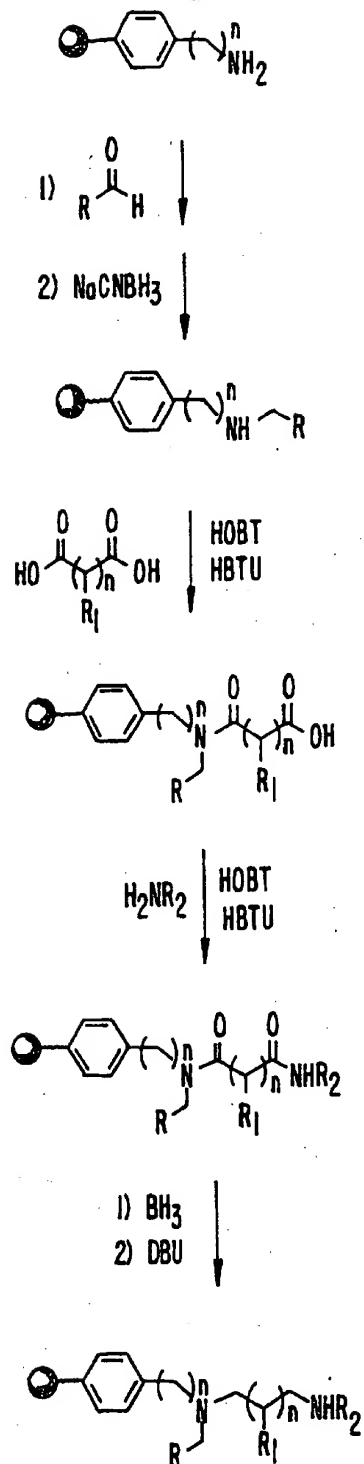
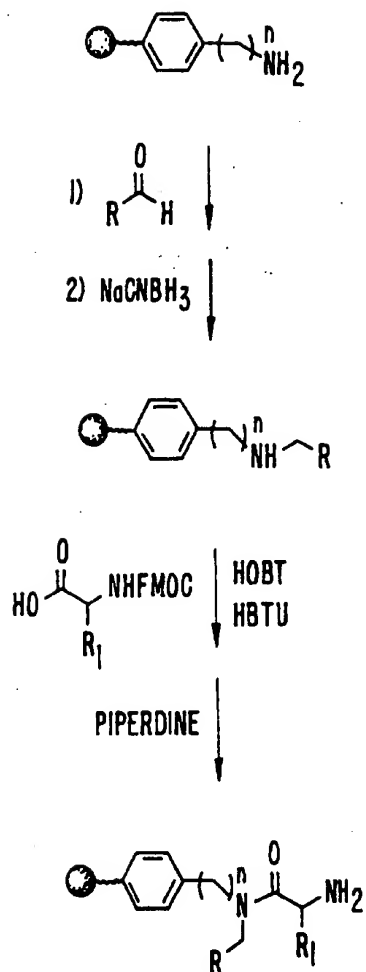
X = OR₅, SR₅, PR₅R₆

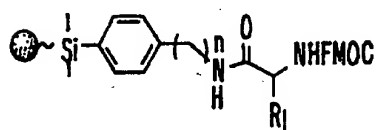
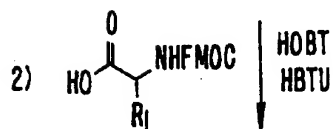
FIG. 4.

6/19

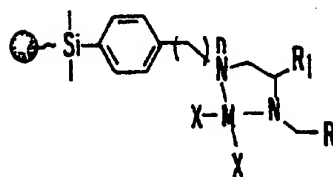
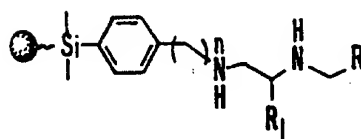
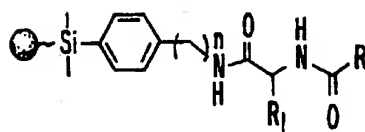
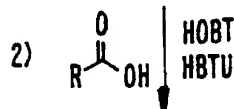
**FIG. 5.**

7/19

**FIG. 6.**

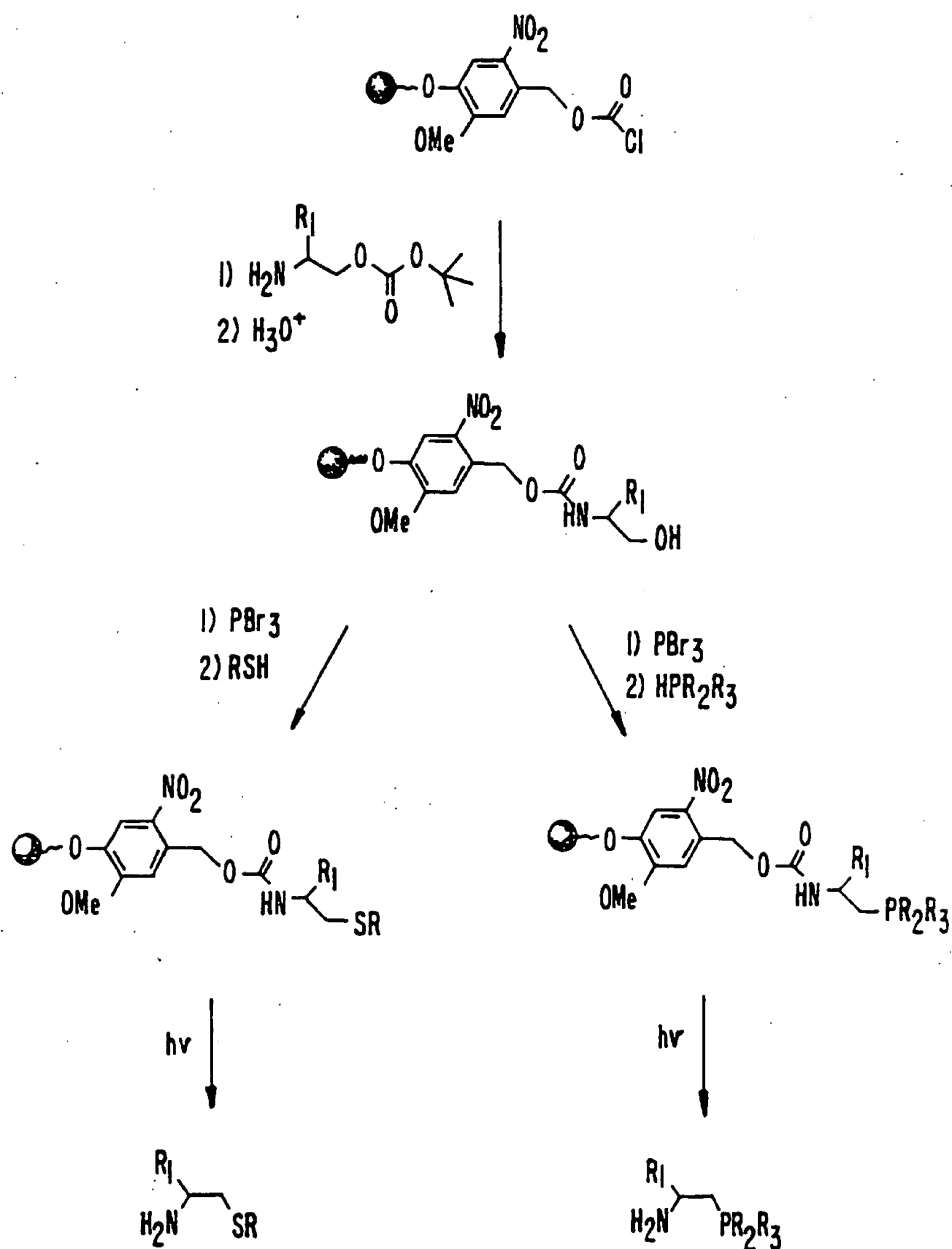
$$\text{Si}(\text{C}_6\text{H}_4)_n\text{NHFMOC}$$


!

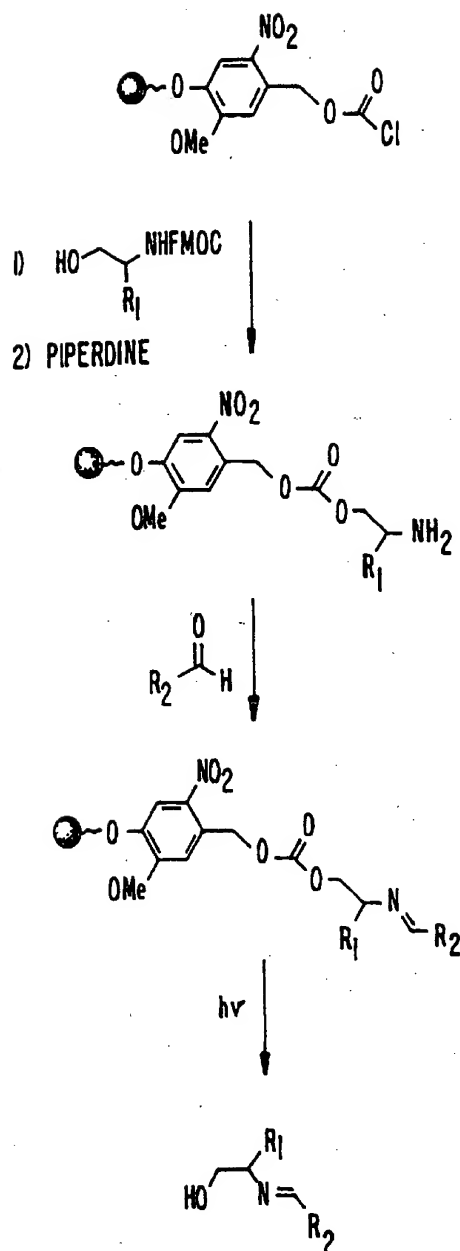


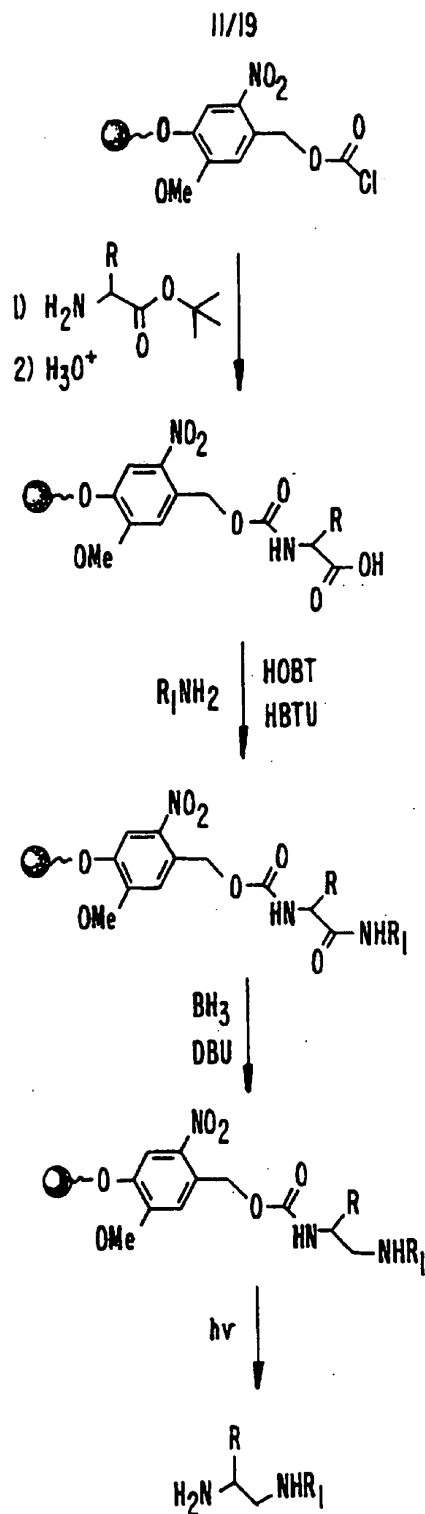
SUBSTITUTE SHEET (RULE 26)

9/19

**FIG. 8.**

10/19

**FIG. 9.**

**FIG. 10.**

12/19

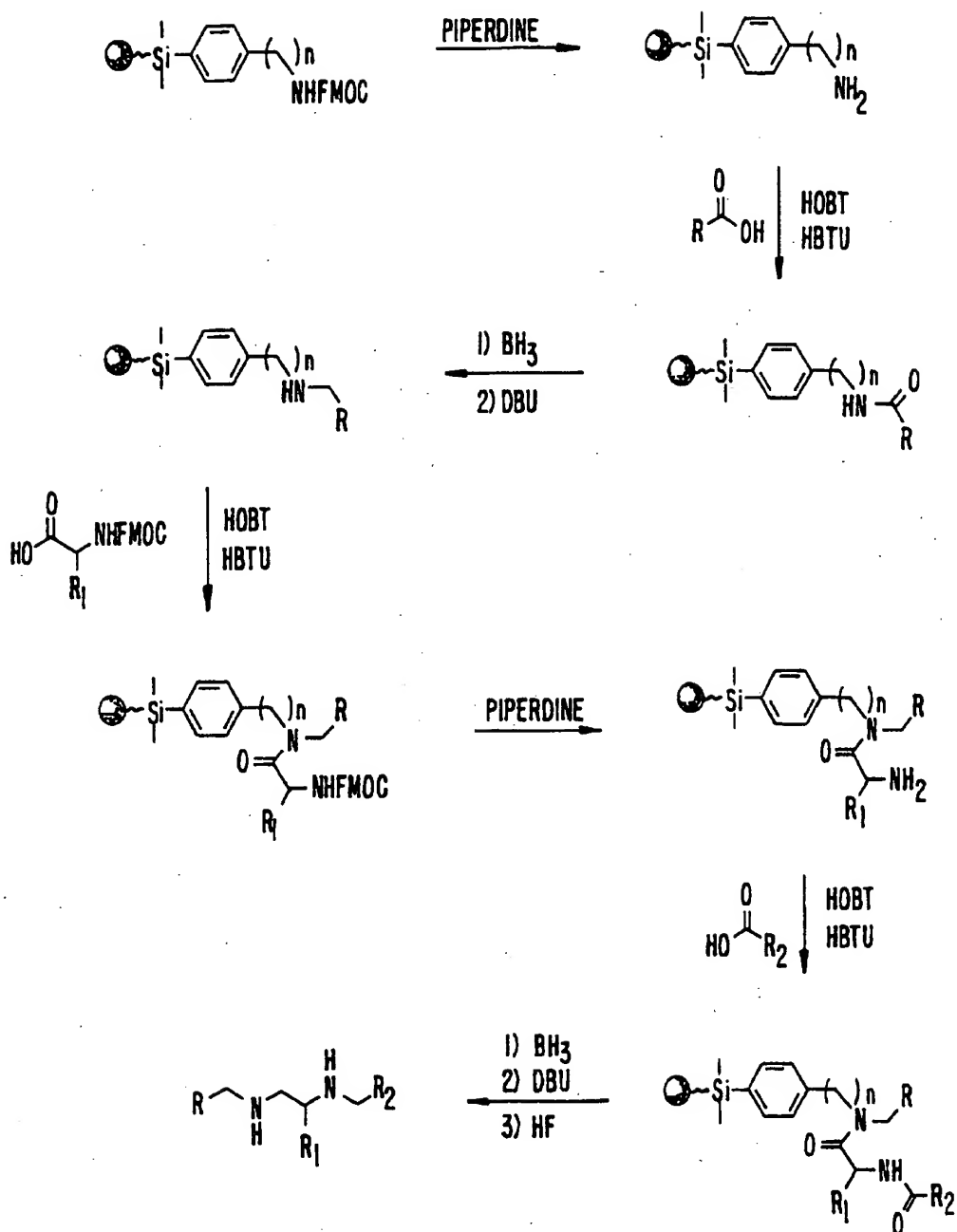


FIG. 11.

13/19

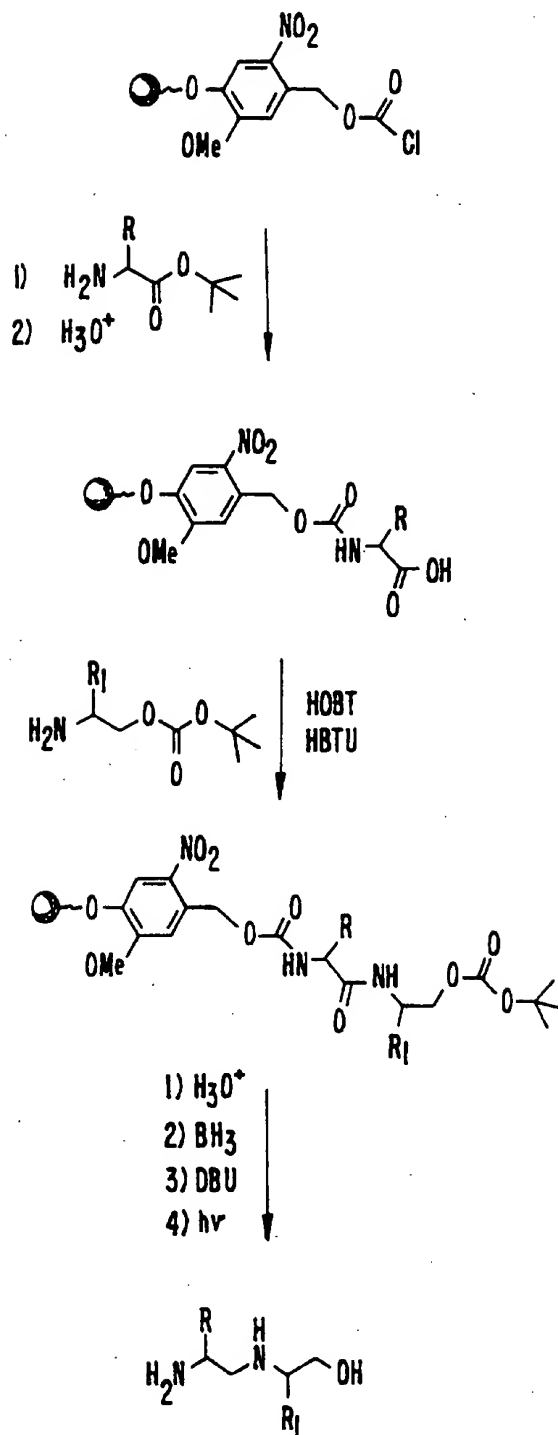
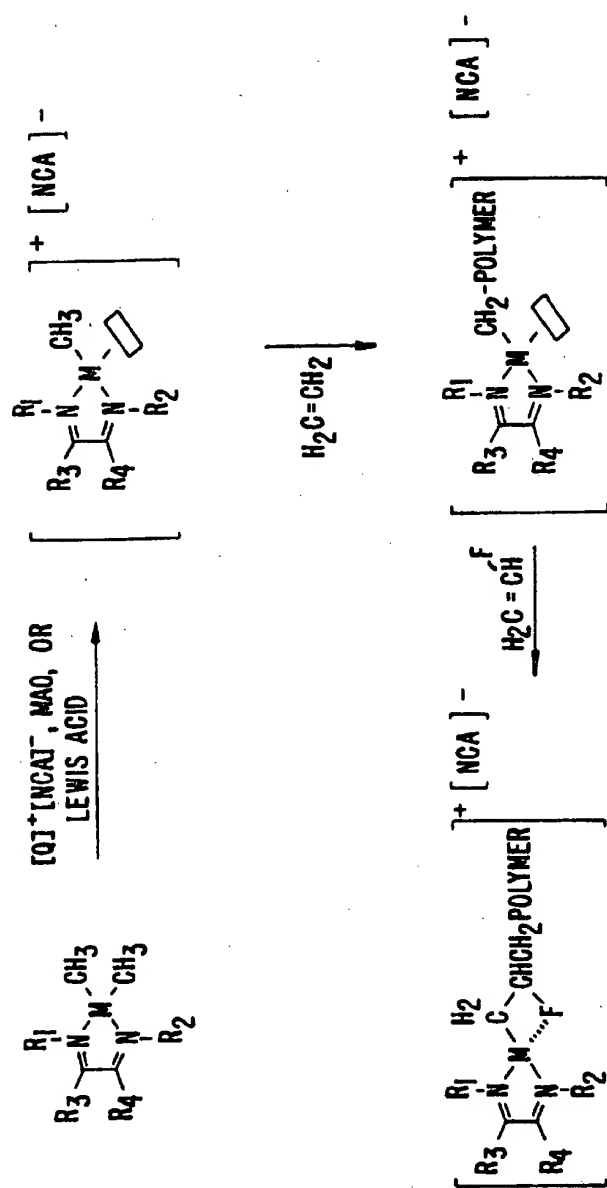


FIG 12.

14/19

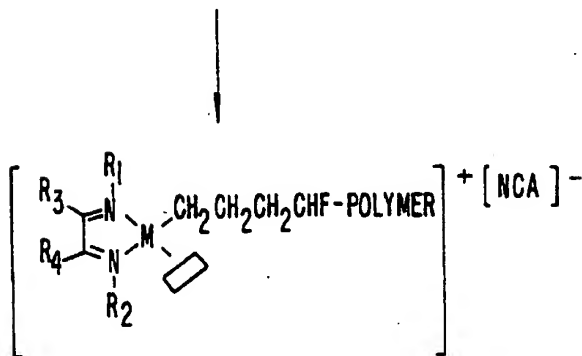
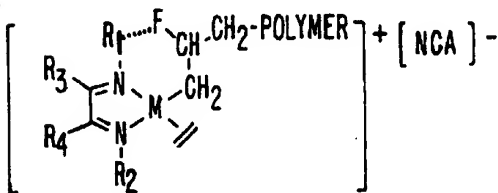
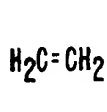
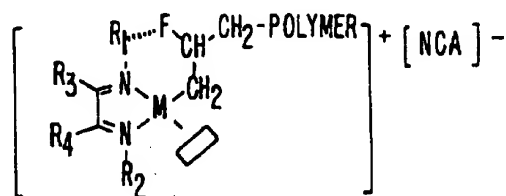


POLAR FUNCTIONALITY (F) CAN CHELATE TO METAL
CENTER AND POTENTIALLY BLOCK VACANT SITE

FIG. 13A.

$$\left[\begin{array}{c} R_1 \\ | \\ R_3 - C = N \\ | \\ R_4 - C = N \\ | \\ R_2 \end{array} \begin{array}{c} H_2 \\ | \\ C \\ | \\ F \end{array} \begin{array}{c} \text{---} \\ \text{---} \\ \text{---} \\ \text{---} \end{array} \begin{array}{c} CH \\ | \\ CH_2 \end{array} \text{--- POLYMER} \right]^+ [NCA]^-$$

11



SUBSTITUTE SHEET (RULE 26)

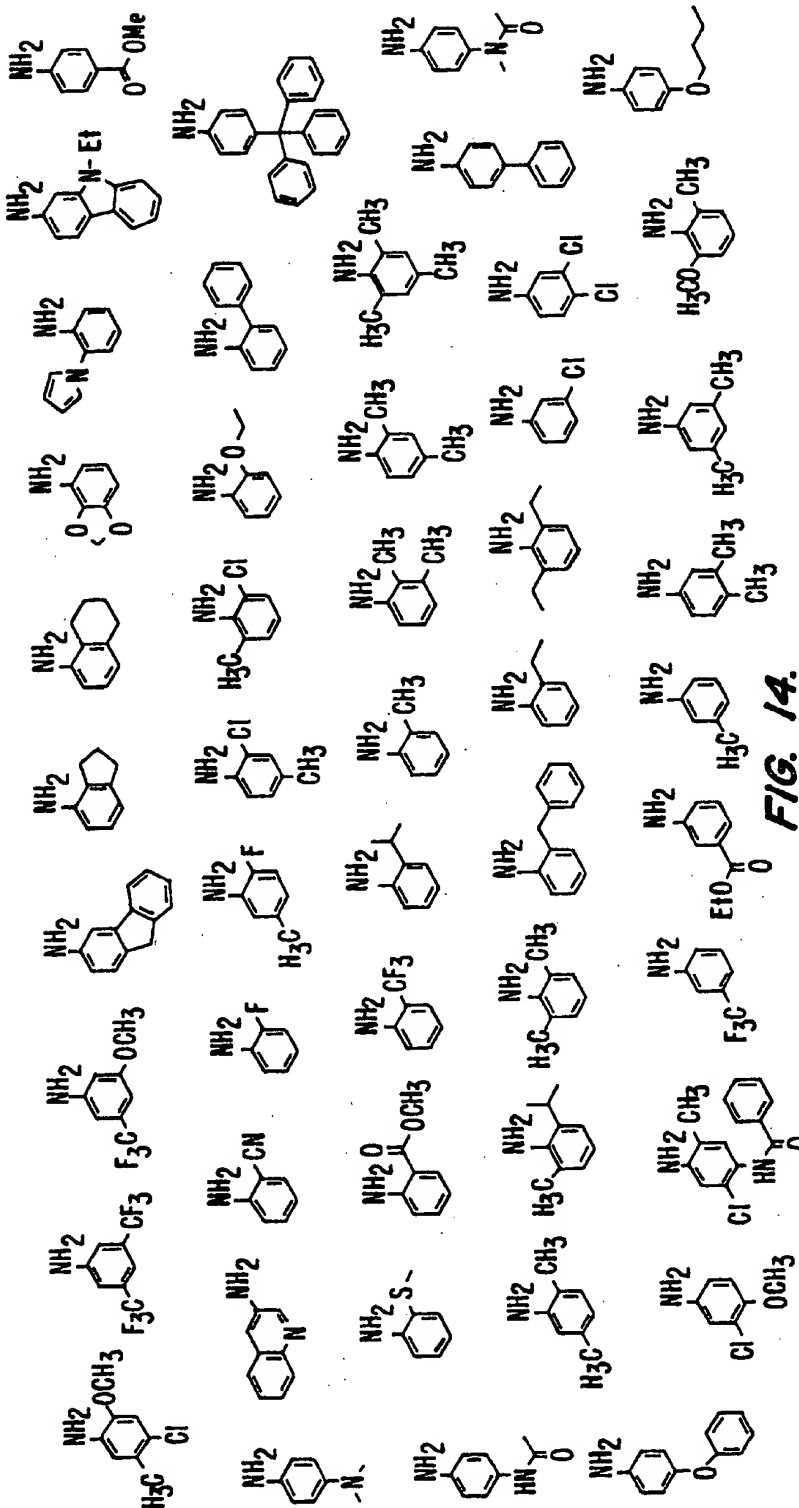


FIG. 14.

17/19

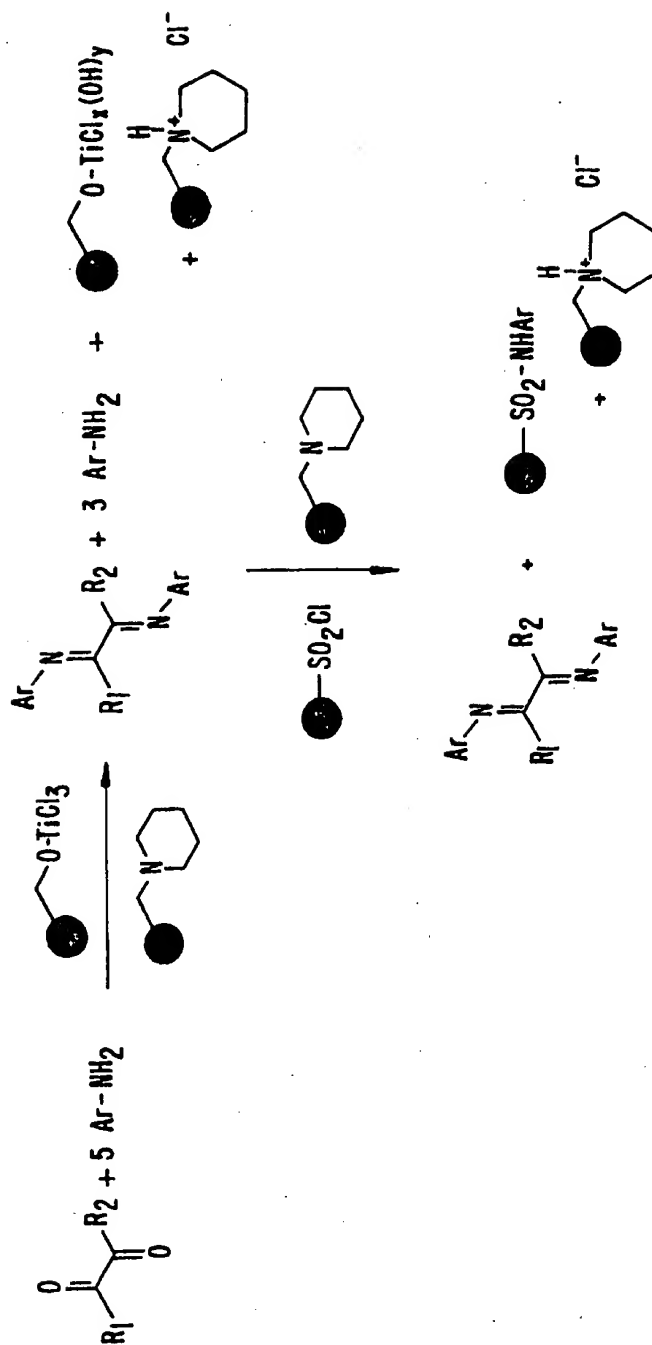


FIG. 15.

18/19

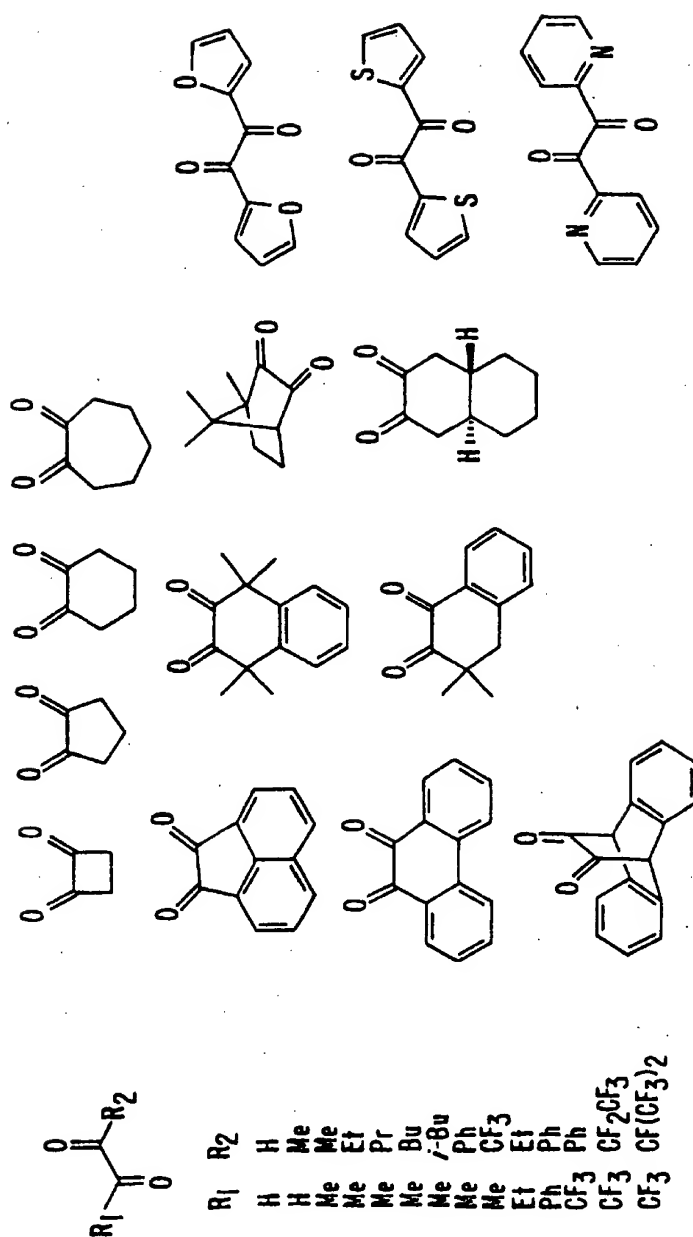
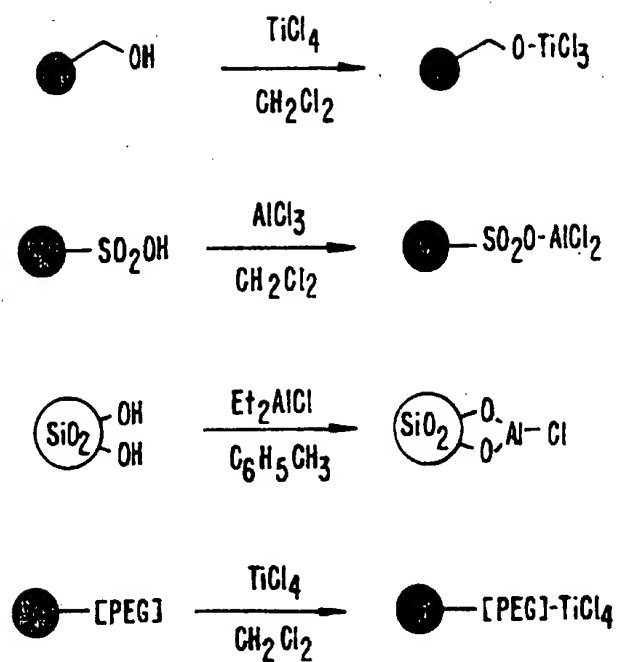


FIG. 16.

19/19

**FIG. 17.**

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/13312

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07F19/00 C07F15/00 C07B61/00 C08F4/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07F C07B C08F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRANCIS: "Combinatorial approach of the discovery of novel coordination complexes" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 118, no. 37, 1996, pages 8983-8984, XP002046206 see the whole document ---	1,3,4, 19,22, 29,36, 40, 59-66, 78, 80-87,89
X	BURGER MATTHEW: "Synthetic ionophores" JOURNAL OF ORGANOMETALLIC CHEMISTRY, - 1995 pages 7382-7383, XP002046207 see the whole document ---	1,3,4, 19,29, 31,36, 59-66, 78,80,89
	-/--	

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 November 1997

Date of mailing of the international search report

09/12/1997

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fischer, B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/13312

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MOATES: "Infrared thermographic screening of combinatorial libraries of heterogeneous catalysts." IND. ENG. CHE. RES., vol. 35, no. 12, 1996, pages 4801-4803, XP002046208 see the whole document -----</p>	1